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Desmopressin for patients with spontaneous intracerebral haemorrhage taking antiplatelet drugs (DASH): a UK-based, phase 2, randomised, placebo-controlled, multicentre feasibility trial

Michael J R Desborough, Rustam Al-Shahi Salman, Simon J Stanworth, Diane Havard, Lisa J Woodhouse, Jennifer Craig, Kailash Krishnan, Paul M Brennan, Robert A Dineen, Tim J Coats, Trish Hepburn, Philip M Bath, Nikola Sprigg, for the DASH trial investigators

Summary

Background The risk of death from spontaneous intracerebral haemorrhage is increased for people taking antiplatelet drugs. We aimed to assess the feasibility of randomising patients on antiplatelet drug therapy with spontaneous intracerebral haemorrhage to desmopressin or placebo to reduce the antiplatelet drug effect.

Methods DASH was a phase 2, randomised, placebo-controlled, multicentre feasibility trial. Patients were recruited from ten acute stroke centres in the UK and were eligible if they had an intracerebral haemorrhage with stroke symptom onset within 24 h of randomisation, were aged 18 years or older, and were taking an antiplatelet drug. Participants were randomly assigned (1:1) to a single dose of intravenous desmopressin 20 µg or matching placebo. Treatment allocation was concealed from all staff and patients involved in the trial. The primary outcome was feasibility, which was measured as the number of eligible patients randomised and the proportion of eligible patients approached, and analysis was by intention to treat. The trial was prospectively registered with ISRCTN (reference ISRCTN67038373), and it is closed to recruitment.

Findings Between April 1, 2019, and March 31, 2022, 1380 potential participants were screened for eligibility. 176 (13%) participants were potentially eligible, of whom 57 (32%) were approached, and 54 (31%) consented and were subsequently recruited and randomly assigned to receive desmopressin (n=27) or placebo (n=27). The main reason for eligible patients not being recruited was the patient arriving out of hours (74 [61%] of 122 participants). The recruitment rate increased after the enrolment period was extended from 12 h to 24 h, but it was then impaired due to the COVID-19 pandemic. Of the 54 participants included in the analysis (mean age 76-4 years [SD 11-3]), most were male (36 [67%]) and White (50 [93%]), 53 (98%) of 54 participants received all of their allocated treatment (one participant assigned desmopressin only received part of the infusion). No participants were lost to follow-up or withdrew from the trial. Death or dependency on others for daily activities at day 90 (modified Rankin Scale score >4) occurred in six (22%) of 27 participants in the desmopressin group and ten (37%) of 27 participants in the placebo group. Serious adverse events occurred in 12 (44%) participants in the desmopressin group and 13 (48%) participants in the placebo group. The most common adverse events were expansion of the haemorrhagic stroke (four [15%] of 27 participants in the desmopressin group and six [22%] of 27 participants in the placebo group) and pneumonia (one [4%] of 27 participants in the desmopressin group and six [22%] of 27 participants in the placebo group).

Interpretation Our results show it is feasible to randomise patients with spontaneous intracerebral haemorrhage who are taking antiplatelet drugs to desmopressin or placebo. Our findings support the need for a definitive trial to determine if desmopressin improves outcomes in patients with intracerebral haemorrhage on antiplatelet drug therapy.

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Introduction

In 2019, approximately 3 million deaths were due to spontaneous intracerebral haemorrhage worldwide.1 Two-thirds of survivors are left dependent on others.2 Approximately a quarter of patients are taking antiplatelet drugs at the time of intracerebral haemorrhage in high-income countries, and this proportion is increasing.3 Prestroke antiplatelet drug use is associated with a 27% relative increase in 1-month case fatality, compared with patients who do not use antithrombotic drugs.4 There is no proven effective drug treatment for intracerebral haemorrhage, although blood pressure lowering might improve outcomes.4 This topic area has been highly prioritised by patient and public involvement groups.5 Desmopressin is a licensed prohaemostatic drug that is commonly used in the treatment of inherited bleeding...
Research in context

Evidence before this study
We searched MEDLINE Ovid (from database inception) and Embase Ovid (from database inception) on Feb 10, 2023, combining search terms for desmopressin, intracerebral haemorrhage, and randomised controlled trials. No language restrictions were applied. Desmopressin reduces bleeding in some settings (eg, patients taking antiplatelet drugs undergoing cardiac surgery) and has a well established role in inherited coagulopathies. No randomised trials have been completed that compared desmopressin with placebo for reversing antiplatelet drug effects in spontaneous intracerebral haemorrhage.

Added value of this study
DASH was designed to demonstrate the feasibility of performing a large randomised trial to assess efficacy of desmopressin for spontaneous intracerebral haemorrhage in patients exposed to antiplatelet drugs. To our knowledge, this is the first randomised trial comparing desmopressin with placebo in patients with intracerebral haemorrhage who are taking antiplatelet drugs. No safety concerns or clinically relevant hyponatraemia occurred.

Methods
Study design and participants
DASH was a phase 2, randomised, placebo-controlled, multicentre feasibility trial. Participants were enrolled by investigators from emergency departments or acute stroke units at ten hospitals in the UK. The trial was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki, and ethics approval was obtained from the East Midlands–Nottingham 2 research ethics committee (18/EM/0184). The DASH trial protocol has been published elsewhere.\textsuperscript{15} Four substantial amendments were planned by the trial management committee, reviewed and supported by the trial steering committee, and approved by the funder and research ethics committee: SA/01/19 (addition of day 90 postal follow-up form); SA/02/19 (change of site principal investigator); SA/03/19 (increase in recruitment time window from 12 h to 24 h after stroke, update to Investigational Medicinal Products storage guidelines, and removal of day 90 questions on postal follow-up questionnaire regarding low sodium and fluid overload); and SA/04/21 (temporary change of chief investigator; closure of one recruiting centre). Ten sites were open to recruitment before the pandemic and before all research was suspended. The study was paused due to the COVID-19 pandemic from March 26, 2020, to June 29, 2020, after which centres reopened according to pre-pandemic levels. To help mitigate the impact of COVID-19 on recruitment, the trial end date was extended from: Dec 31, 2020, to Dec 31, 2021 (costed extension), and Dec 31, 2021, to June 30, 2022 (no-cost extension).

Patients were included in the trial if they met all inclusion criteria and no exclusion criteria. Inclusion criteria were that the patient was an adult (aged ≥18 years), with intracerebral haemorrhage confirmed on brain CT, and prescribed and thought to be taking a daily oral antiplatelet drug in the preceding 7 days (ie, cyclooxygenase inhibitors, phosphodiesterase inhibitors, or P2Y\textsubscript{12} inhibitors). In the initial version of the protocol, patients were eligible if they could undergo randomisation within 12 h of symptom onset. After a substantial amendment (SA/03/19 on Nov 22, 2019) due to slow enrolment, participants could be
recruited if they could undergo randomisation within 24 h from onset of symptoms. Exclusion criteria were known secondary causes of intracerebral haemorrhage, patients at risk of fluid retention, systolic blood pressure of less than 90 mm Hg, known drug-eluting stent in previous 3 months, allergy to desmopressin, pregnant or breast-feeding, life expectancy of less than 4 h or planned for palliative care only, Glasgow Coma Scale score of less than 5, and modified Rankin Scale score of more than 4.

Patients with the capacity to give informed written consent were approached directly; otherwise, a relative or close friend was approached for consent. If a relative or friend could not be identified, a professional representative (ie, doctor) not associated with the trial could be approached for proxy consent. Patients were approached again for consent when they regained capacity. This procedure is in accordance with emergency consent approvals.

Randomisation and masking
Participants were randomised centrally to receive either desmopressin or placebo (1:1), with a 5% random flip, using a computer-generated randomisation sequence in a real time. Treatment allocation was concealed from all staff and participants in the trial. Randomisation involved minimisation on key prognostic risk factors: age (>70 years); sex (male); time since onset (≥3 h); systolic blood pressure (≥170 mm Hg); and presence (or no information on presence or absence) of intraventricular haemorrhage. Randomisation allocated a number corresponding to a treatment pack and the participant received treatment from the allocated numbered pack. It was considered not possible to mask personnel preparing the injection for administration to the treatment allocation because the ampoules of active and placebo injections were different and carried the manufacturer’s identifying information. Clinicians, patients, and outcome assessors (ie, clinical, radiological, and haematological assessors) were blinded to treatment allocation.

Procedures
Participants allocated desmopressin received a 20 μg dose intravenously. Desmopressin (Ferring Pharmaceuticals, West Drayton, UK) was supplied in 1 mL glass ampoules at a concentration of 4 μg/mL; five ampoules were added to 50 mL sodium chloride 0·9%, and the infusion was done intravenously. Desmopressin should be stored at 2–8°C. We developed a pharmacy manual such that desmopressin or placebo was quarantined in the event the storage temperature was less than 2°C or higher than 8°C for 28 days cumulatively (as per stability data) or any temperature higher than 25°C. We summarised temperature excursions, including total number of temperature excursions, number of desmopressin or placebo packs that were exposed, quarantined, or destroyed, and the number of participants receiving desmopressin or placebo who had been exposed to temperature excursion. Although not listed as a specific outcome in the protocol, the incidence of temperature excursions contributes to the overall assessment of feasibility and is presented.

Sites were required to complete screening logs for consecutive patients with intracerebral haemorrhage. Participants’ age, sex, medical history, antiplatelet drug use, intracerebral haemorrhage location, intraventricular haemorrhage, and modified Rankin scale score were obtained at baseline by local investigators. Participants were reviewed again on day 2, at hospital discharge, and on day 90 to gather information on interventions, adverse events, discharge date, and discharge destination (eg, patient’s own home or to nursing home care).

At day 90, central assessors trained in administering the appropriate questionnaires, and who were masked to treatment allocation, followed up each participant by telephone. Questionnaires administered were the Barthel index (to measure disability; 0–100, with 0 indicating severe disability and 100 indicting no disability), the modified Rankin scale (to measure functional independence; 0–6, with 0 indicating no disability through to 6 indicating death), the EuroQol-5D health state utility and visual analogue scale (to measure quality of life), the telephone interview for cognitive status-modified (to assess cognition), and the Zung depression scale (to assess mood). Serious adverse events were also reported by telephone up to day 90 (and could be reported at any time).

Brain imaging (CT head scan) was performed before randomisation and 24 h after administration of the allocated treatment to measure haematoma volume. Haematoma volume was measured centrally, by a trained assessor who was masked to treatment allocation, using semi-automated segmentation. Haematoma expansion was defined as an absolute increase in haematoma volume of greater than 6 mL or relative growth of greater than 33%.

To assess baseline platelet function, platelets were stimulated with arachidonic acid or adenosine diphosphate. Platelet cell surface P-selectin expression was then measured using a standardised assay (Platelet Solutions, Nottingham, UK) to assess retrospectively whether patients were taking antiplatelet drugs, as previously
described (appendix p 5). Von Willebrand factor antigen (VWF Ag Kit, Siemens, Marburg, Germany), Von Willebrand factor activity (Innovance VWF Ac kit, Siemens, Marburg, Germany), and chromogenic factor VIII were measured centrally, at baseline and 1 h after allocated treatment, by assessors who were masked to treatment allocation. Serum sodium was assessed locally 24 h after administration of the desmopressin or placebo, and these results were made available to the clinical team. Hyponatraemia was defined as a sodium concentration less than 135 mmol/L. Moderate to severe hyponatraemia was defined as a sodium concentration less than 125 mmol/L.

Outcomes
The primary outcome measures of this feasibility trial were the proportion of eligible patients who were enrolled and received their allocated treatment, the proportion of eligible patients who underwent randomisation (and reasons for non-randomisation), the proportion of screened patients who were eligible, the rate of participant recruitment per month per site, time to randomisation after hospital admission, adherence to the allocated treatment, the proportion of participants followed up to 90 days (and reasons for loss to follow up), and the proportion of randomised participants with full outcome data available (and reasons for non-availability of data).

Secondary outcomes were change in haematoma volume at 24 h (including changes meeting the definition of haematoma expansion), hyponatraemia at 24 h, length of hospital stay, discharge destination, death or dependency at day 90 (modified Rankin scale score >4), mortality within 28 days and up to day 90, serious adverse events up to day 90 (including thromboembolic events), disability at day 90 (Barthel index), quality of life at day 90 (EuroQol), cognition at day 90 (telephone interview for cognitive status-modified), and mood at day 90 (Zung depression scale). Other secondary outcome measures were baseline platelet dysfunction (measured by P-selectin assay), and change in factor VIII, Von Willebrand factor antigen, and Von Willebrand factor activity at 1 h after administration of desmopressin or placebo. The manufacturer of the P-selectin assay closed their business before the end of the trial, so analysis of this outcome in all participants was not completed. A protocol-defined health economic assessment will be reported separately.

All adverse events on day 1 (including during infusion) and for the 24-h period after dose administration were collected. All adverse events were assessed for seriousness, expectedness, and causality by adjudicators masked to treatment allocation. Serious adverse events were categorised in accordance with the Medical Dictionary for Regulatory Authorities. Serious adverse events occurring within the first 7 days were assessed for seriousness, expectedness, and causality. Fatal serious adverse events and safety outcome events (eg, fluid overload and hyponatraemia) were reported until day 90.

Statistical analysis
No formal sample size was calculated because this study was a feasibility trial to inform potential recruitment rates for a definitive trial. However, we considered that if more than 50 participants were randomised from ten centres in a 12-month period, it would be probable that, assuming similar recruitment rates in additional centres, a larger study recruiting approximately 1200 participants in around 50 centres recruiting for 60 months would be feasible.

Data were analysed by a qualified statistician, using a validated software package (SAS version 9.4). A statistical analysis plan (SAP) was agreed on before database lock and release of randomisation codes. An independent data monitoring committee reviewed the data during the trial on July 14, 2019 (n=3), and March 13, 2020 (n=24). A further Chairman’s review was conducted on Oct 4, 2021 (n=44).

All available data were used, including overall numbers of patients presenting to the participating hospital stroke services and screening data. Sites completed and returned monthly screening logs on consecutive patients with intracerebral haemorrhage and included ineligibility or reasons for non-inclusion. When summaries by treatment group were provided, these were based on an intention-to-treat population, with the exception of safety data. A safety population was defined to summarise the safety data in this study, and these participants were summarised according to the treatment they received irrespective of randomisation. Variables were summarised by treatment group, using summary statistics. Counts were summarised using n (%), and continuous variables were summarised using mean (SD) or median (IQR) depending on their distribution.

Because the proposed primary efficacy outcome in a definitive trial would be death or dependency at day 90, measured using the modified Rankin scale, we compared between treatment groups the full modified Rankin scale at day 90, using unadjusted ordinal logistic regression, and death and dependency at day 90 (modified Rankin scale score >4), using unadjusted binary logistic regression. Results of these analyses are reported as odds ratios (ORs) with corresponding 95% CIs. No formal statistical comparisons were made for any of the other outcome measures. The occurrence of missing data was also reported, with no imputation of missing data.

The DASH trial was prospectively registered with ISRCTN, ISRCTN67038373.

Role of the funding source
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.
Results
Between April 1, 2019, and March 31, 2022, 1380 potential participants were screened for eligibility at ten hospitals in the UK (appendix p 1). After the pandemic, 13 participants were potentially eligible but not approached for recruitment due to sites being on hold, no investigational product being available, or not having capacity, compared with no eligible patients missed for these capacity reasons before the pandemic. 1204 (87%) of 1380 participants were considered ineligible. The most common reasons for ineligibility were no history of antiplatelet use (843 [70%] participants) or presentation to hospital more than 24 h after symptom onset (152 [13%] participants; appendix p 2). 176 (13%) of 1380 participants were potentially eligible, of whom 57 (32%) were approached for consent. 54 (31%) consented and were subsequently recruited and underwent randomisation (figure 1). The most common reasons for the 122 eligible patients not being recruited were the patients arriving out of hours (74 [61%] participants), no doctor being available (17 [14%] participants), and recruitment being on hold (ten [8%] participants; appendix p 4). Patients who were missed were potentially eligible but were not recruited.

Patient consent was obtained from 23 (43%) of 54 participants before enrolment in the trial. Proxy consent was used for the other 31 (57%) participants and was provided by personal nominees for 27 (50%) and by professional legal nominees for four (7%).

Participant characteristics are summarised in table 1. Of the 54 participants included in the analysis (mean age 76·4 years [SD 11·3]), 36 (67%) were male and 50 (93%) were White. The median time from stroke onset to randomisation across all sites was 10·2 h [IQR 4·5–16·3; placebo 9·5 h [IQR 4·3–17·6]). The rate of recruitment increased after the enrolment time was extended from 12 h to 24 h. 14 patients were enrolled in 8 months at ten sites (1·8 patients per month) after the amendment and 11 patients were enrolled in 4 months (2·8 patients per month) before the amendment, and 176 (13%) of 1380 participants were screened for eligibility at ten hospitals in the UK (appendix p 1). After the pandemic, 13 participants were potentially eligible but not approached for recruitment due to sites being on hold, no investigational product being available, or not having capacity, compared with no eligible patients missed for these capacity reasons before the pandemic. 1204 (87%) of 1380 participants were considered ineligible. The most common reasons for ineligibility were no history of antiplatelet use (843 [70%] participants) or presentation to hospital more than 24 h after symptom onset (152 [13%] participants; appendix p 2). 176 (13%) of 1380 participants were potentially eligible, of whom 57 (32%) were approached for consent. 54 (31%) consented and were subsequently recruited and underwent randomisation (figure 1). The most common reasons for the 122 eligible patients not being recruited were the patients arriving out of hours (74 [61%] participants), no doctor being available (17 [14%] participants), and recruitment being on hold (ten [8%] participants; appendix p 4). Patients who were missed were potentially eligible but were not recruited.

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Secondary outcome data are summarised in table 2. One (4%) patient in the placebo group required neurosurgery. Median change in haematoma volume at 24 h was 0 mL (IQR −1·4 to 2·0) in the desmopressin group and 0·5 mL (IQR 0·2 to 1·7) in the placebo group. Median length of hospital stay was 9 days (IQR 3–15) in the desmopressin group and 6 days (2–22) in the placebo group. Five patients in each treatment group died before 28 days. At day 90, in the desmopressin group, 18 (67%) patients had been discharged home, four (15%) were in hospital or residential care, and five (19%) had died. In the placebo group, 16 (59%) patients were at home, four (15%) were in hospital or residential care, and seven (26%) had died. Death or dependency at day 90 (modified Rankin Scale score >4) occurred in six (22%) of 27 participants in the desmopressin group and ten (37%) of 27 participants in the placebo group. Shift in modified Rankin Scale score is summarised in figure 2. No difference was seen between the treatment groups for either the full-scale modified Rankin Scale score (OR 0·74 [95% CI 0·29–1·93]; table 2), or death and dependency (OR 0·49 [95% CI 0·15–1·61]; table 2).

Serious adverse events had occurred by day 90 in 12 (44%) of 27 participants in the desmopressin group and 13 (48%) of 27 participants in the placebo group. After 24 h, mild hyponatraemia (sodium concentration 125–134 mmol/L) was present in eight (35%)
of 23 participants in the desmopressin group and three (13%) of 24 participants in the placebo group. No patient in either group had a sodium concentration of less than 125 mmol/L. Thrombotic events were reported for one (4%) patient in the desmopressin group (non-ST-elevation myocardial infarction) and
one (4%) patient in the placebo group (ischaemic stroke; table 3).

At day 90, the mean Barthel index score was 71·6 (SD 33·1) in the desmopressin group (n=22), and 67·4 (33·6) in the placebo group (n=19). Mean EuroQol-5D was 0·37 (SD 0·40) in the desmopressin group (n=27) and 0·34 (SD 0·35) in the placebo group (n=26). Mean score on the telephone interview for cognitive status-modified score was 22·3 (SD 6·4) in the desmopressin group and 22·9 (4·0) in the placebo group. The mean Zung depression scale score was 52·2 (SD 15·5) in the desmopressin group and 45·0 (10·4) in the placebo group.

The first 28 patients recruited into the DASH trial were eligible for P-selectin testing, and the tests were done in 14 (50%). Table 4 presents results of haemostatic marker testing at baseline and 1 h after treatment. Changes from baseline to 1 h in these markers were greater in the desmopressin group than with placebo.

**Discussion**

The findings of the DASH trial showed the feasibility of running a large randomised trial of desmopressin in patients on antiplatelet drug therapy with intracerebral haemorrhage. 176 (13%) of 1380 patients with intracerebral haemorrhage were eligible for the DASH trial. Of these, 54 (31%) participants were recruited. The measures in place to follow up participants worked well, and no patients were lost to follow-up. Desmopressin and placebo infusions were administered in full for all but one participant. No safety concerns, such as thrombosis, were reported. Hyponatraemia is a known side-effect of desmopressin, and our results showed the incidence of

<table>
<thead>
<tr>
<th>Outcomes measured at 24 h</th>
<th>All participants (n=54)</th>
<th>Desmopressin group (n=27)</th>
<th>Placebo group (n=27)</th>
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<tbody>
<tr>
<td>Sodium concentration, mmol/L</td>
<td>136·9 (4·1); n=47</td>
<td>135·6 (3·6); n=23</td>
<td>138·1 (4·2); n=24</td>
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<tr>
<td>Any hyponatraemia, &lt;125 mmol/L</td>
<td>11 (23%); n=47</td>
<td>8 (35%); n=23</td>
<td>3 (13%); n=24</td>
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<td>0; n=23</td>
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<th>Outcomes measured at discharge</th>
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<td>Length of hospital stay, days</td>
<td>8·0 (3·0–15·0)</td>
<td>9·0 (3·0–15·0)</td>
<td>6·0 (2·0–22·0)</td>
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<td>Discharge destination</td>
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<tr>
<td>Home, independent</td>
<td>17 (4%); n=42</td>
<td>11 (5%); n=22</td>
<td>6 (3%); n=20</td>
</tr>
<tr>
<td>Home, needing care</td>
<td>17 (4%); n=42</td>
<td>7 (32%); n=22</td>
<td>10 (5%); n=20</td>
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<tr>
<td>Hospital, rehabilitation</td>
<td>5 (12%); n=42</td>
<td>3 (14%); n=22</td>
<td>2 (1%); n=20</td>
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<tr>
<td>Hospital, readmission</td>
<td>2 (5%); n=42</td>
<td>0; n=22</td>
<td>2 (1%); n=20</td>
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<tr>
<td>Hospital, not discharged</td>
<td>1 (2%); n=42</td>
<td>1 (5%); n=22</td>
<td>0; n=20</td>
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<th>Outcomes measured at day 90</th>
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<tr>
<td>Modified Rankin Scale score*</td>
<td>4·0 (3·0–5·0)</td>
<td>4·0 (3·0–4·0)</td>
<td>4·0 (3·0–6·0)</td>
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<td>0</td>
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</tr>
<tr>
<td>1</td>
<td>5 (9%)</td>
<td>2 (7%)</td>
<td>3 (11%)</td>
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<td>6 (11%)</td>
<td>4 (15%)</td>
<td>2 (7%)</td>
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<td>14 (26%)</td>
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<td>7 (26%)</td>
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<td>13 (24%)</td>
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<td>5 (19%)</td>
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<td>5</td>
<td>4 (7%)</td>
<td>1 (4%)</td>
<td>3 (11%)</td>
</tr>
<tr>
<td>6</td>
<td>12 (22%)</td>
<td>5 (19%)</td>
<td>7 (26%)</td>
</tr>
<tr>
<td>Death or dependency (modified Rankin Scale score &gt;4)†</td>
<td>16 (3)</td>
<td>6 (22%)</td>
<td>10 (37%)</td>
</tr>
<tr>
<td>Barthel index</td>
<td>69·6 (33·0); n=41</td>
<td>71·6 (33·1); n=22</td>
<td>67·4 (33·6); n=19</td>
</tr>
<tr>
<td>EuroQol-5D health state utility</td>
<td>0·36 (0·37); n=53</td>
<td>0·37 (0·40); n=27</td>
<td>0·34 (0·35); n=26</td>
</tr>
<tr>
<td>EuroQol visual analogue scale</td>
<td>62·5 (17·9); n=37</td>
<td>62·0 (19·5); n=20</td>
<td>65·2 (16·3); n=17</td>
</tr>
<tr>
<td>Telephone interview for cognitive status-modified</td>
<td>22·5 (5·4); n=26</td>
<td>22·3 (6·4); n=15</td>
<td>22·9 (4·0); n=11</td>
</tr>
<tr>
<td>Zung depression scale</td>
<td>49·1 (13·8); n=28</td>
<td>52·2 (15·5); n=16</td>
<td>45·0 (10·4); n=12</td>
</tr>
<tr>
<td>Mortality</td>
<td>12 (22%)</td>
<td>5 (19%)</td>
<td>7 (26%)</td>
</tr>
<tr>
<td>At 28 days</td>
<td>10 (19%)</td>
<td>5 (19%)</td>
<td>5 (19%)</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>25 (46%)</td>
<td>12 (44%)</td>
<td>3 (11%)</td>
</tr>
<tr>
<td>Thrombotic events</td>
<td>2 (4%)</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Change in haematoma volume, mL</td>
<td>0·1 (–1·3 to 2·1); n=46</td>
<td>0·0 (–1·4 to 2·0); n=24</td>
<td>0·5 (–0·7 to 2·1) n=22</td>
</tr>
<tr>
<td>Haematoma expansion‡</td>
<td>10 (22%); n=46</td>
<td>5 (21%); n=24</td>
<td>5 (23%); n=22</td>
</tr>
</tbody>
</table>

**Table 2: Secondary outcome measures**

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mild hyponatraemia was higher for those treated with desmopressin, with no instances of moderate or severe hyponatraemia, suggesting its safety in this clinical setting. To our knowledge, the DASH trial is the first randomised trial to compare desmopressin with placebo in patients on antiplatelet drug therapy with...
intracerebral haemorrhage. A 2021 systematic review identified three retrospective controlled studies (including 263 patients in total) assessing desmopressin in intracerebral haemorrhage. No randomised controlled trials have been done since this systematic review, although further case series have been published.

The proposed primary efficacy outcome in a definitive trial would be death or dependency at day 90, measured using the modified Rankin scale. For a definitive study, we estimate approximately 1500 eligible patients would need to be recruited, a recruitment rate of up to 500 participants per year in the UK. Notably, DASH was conducted before, during, and after the global COVID-19 pandemic, during which time staff were redeployed to work in alternative areas. Therefore, the participant recruitment rate for a definitive trial could be increased from that observed in DASH. Furthermore, a future clinical trial to assess efficacy would be most likely to be successful if it were embedded into clinical practice, which would increase recruitment because it would be possible for clinical teams to randomly assign patients out of hours. In a definitive trial, a more pragmatic approach to temperature monitoring should be used, requiring that desmopressin be stored in a fridge, in line with current clinical practice.

A pragmatic decision was made in the DASH trial to administer desmopressin or placebo as soon as possible after diagnosis, but to allow enrolment up to 24 h after symptom onset for patients who presented late or for whom enrolment was not possible in the first few hours. This decision is in contrast to ongoing trials of prohaemostatic drugs, such as the FASTEST trial of recombinant factor VIIa (NCT01946883) and the TICH-3 trial of tranexamic acid (ISRCTN97969350), in which much tighter periods (2 h and 4·5 h, respectively) have been selected. There is growing awareness that the greatest risk of haematoma expansion occurs early after intracerebral haemorrhage, with previous clinical trials suggesting administration of prohaemostatic therapy occurred too late after stroke onset to improve outcome. Although the risk of haematoma expansion is greatest in the first few hours after intracerebral haemorrhage onset, it can occur for the first 24 h, particularly in patients on antiplatelet therapy. The largest systematic review, including 30000 patients with intracerebral haemorrhage on antiplatelet therapy from 23 studies, reported that such patients had larger baseline haematoma volume and were more likely to have haematoma expansion over 24 h compared with patients not on antiplatelet drugs (haematoma expansion OR 2·58 (95% CI 1·18–5·67), but not beyond this timepoint. In TICH-2, 165 (35%) of 611 patients with intracerebral haemorrhage on antiplatelet treatments underwent haematoma expansion after enrolment (mean 4·1 h) within the first 24 h.

Several mechanisms have been proposed for how desmopressin might potentially reduce bleeding for patients on antiplatelet drugs. For instance, desmopressin stimulates release of Von Willebrand factor and factor VIII from endothelial Weibel-Palade bodies. Von Willebrand factor causes platelet adhesion to collagen through platelet glycoprotein Ib-V-IX receptors, and might also bind platelets together directly through their glycoprotein IIIb/IIia receptors. Increased concentrations of Von Willebrand factor, therefore, have the potential to compensate for the platelet function defect associated with antiplatelet drugs. Another suggested mechanism is that desmopressin might increase the formation of procoagulant platelets. Participants treated with desmopressin had a greater increase in Von Willebrand factor and factor VIII than did those treated with placebo, although no formal statistical comparison was made.

Guidelines currently provide conflicting guidance on use of desmopressin for patients on antiplatelet drugs with intracerebral haemorrhage. The Neurocritical Care Society and Society of Critical Care Medicine recommend a single dose of 0·4 µg/kg desmopressin for patients with intracranial haemorrhage who were exposed to antiplatelet agents; for patients undergoing a neurosurgical procedure, these guidelines recommend that desmopressin can be used in addition to platelet transfusion. The American Heart Association and American Stroke Association advise that further studies are necessary to determine if there is a subgroup of patients taking antiplatelet drugs with intracerebral haemorrhage who might benefit from desmopressin.

The DASH trial has several strengths. First, it provides randomised data for the use of desmopressin for acute intracerebral haemorrhage. Second, the methodology of the trial was rigorous, and the feasibility of the approach under investigation was demonstrated. Finally, there is substantial worldwide mortality and a large morbidity
We declare no competing interests.

Declaration of interests and LJW directly accessed and verified the underlying data reported in responsibility for the decision to submit for publication. MJRD, NS, All authors had full access to all the data in the study and had final management. LJW and TH did the statistical analysis. PMBr, RAD, the first draft of the manuscript with NS. DH and JC provided trial management. KK and RD centrally assessed the imaging. 

Finally, the six patients who were taking dual antiplatelet therapy were all randomised to placebo. In a large definitive trial, we would consider minimisation on additional prognostic factors, such as antiplatelet therapy and baseline stroke severity.

In summary, given sufficient recruiting centres and pragmatic trial methodology, it should be feasible to conduct a definitive trial to determine if desmopressin improves outcomes in patients on antiplatelet drug therapy with intracerebral haemorrhage. Although this trial could be delivered as a standalone study, it might be more efficient as part of a platform trial or to embed in an existing intracerebral haemorrhage trial. Given the high mortality and morbidity after intracerebral haemorrhage in patients exposed to antiplatelet drugs, and the increased frequency of patients taking antiplatelet drugs, even a small reduction in morbidity or mortality could reduce the risk of death and leave tens of thousands of patients free from disability.

Contributors
MJRD, SJ, RA-SS, and NS had the ideas for the study. MJRD wrote the first draft of the manuscript with NS. DH and JC provided trial management. LJW and TH did the statistical analysis. PMBr, RAD, TJ, and PMBb provided expert input in trial design. MJRD oversaw the laboratory analysis. KK and RD centrally assessed the imaging. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. MJRD, NS, and LJW directly accessed and verified the underlying data reported in the manuscript.

Declaration of interests
We declare no competing interests.

Data sharing
The trial chief investigators (MJRD and NS) will consider requests to share anonymised individual participant data via email at dash@nottingham.ac.uk. Submitted requests will require a protocol detailing hypothesis, aims, analyses, and intended tables and figures. Where possible, we will perform the analyses; alternatively, deidentified data and a data dictionary will be supplied for the necessary variables for promote analysis. Any sharing will be subject to a signed data access agreement. Individual participant data will eventually be shared with the Virtual International Stroke Trials Archive (VISTA) collaboration.

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References


