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Safety and efficacy of minimally invasive surgery plus recombinant tissue plasminogen activator in intracerebral haemorrhage evacuation (MISTIE): a randomised, phase 2 trial

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Contributions. DFH and MZ organized the trial hypotheses, designed the trial, and provided guidance about the data analysis and interpretation/presentation of the data. DFH drafted most of the sections of the manuscript. EFA, CW, WCB, RSG, RD, JLC, JH, PC, PV, NM, IA, ADM, BG, PK, KL, and NMcB were involved in the design of the study and provided contributions to the writing and revising of the manuscript. KL, NMcB, SWM, and AJBH organized and managed the trial including trial start-up, data collection, quality assurance, and trial close-out. DG, TCM, NU, and WAM provided the region of interest calculations for all volumetric measurement results. WZ, CK, and JRC provided independent review and adjudication of all safety events. RET, JM, MR, CBT, GY, and EH were involved in the statistical analysis, data interpretation, and contributed to the development and revisions to the manuscript. SJ provided critical review of the manuscript. The MISTIE II investigators contributed equally to the identification and, when eligible, randomization of trial participants.

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SUMMARY

Background—Craniotomy, when evaluated in trials, does not improve outcome after intracerebral haemorrhage (ICH). Whether minimally invasive catheter evacuation followed by thrombolysis is safe and can achieve a good functional outcome by removing clot is unknown. We investigated safety and efficacy of alteplase with minimally invasive surgery (MIS) in patients with intracerebral haemorrhage.

Methods—MISTIE was an international, randomized, open-label study and was done in 26 hospitals in the USA, Canada, the UK, and Germany. Patients (aged 18–80 years), with non-traumatic (spontaneous) ICH ≥20 mL were randomly allocated, centrally, to medical care or image-guided MIS plus rt-PA (0.3 mg or 1.0 mg every 8 hours for up to 9 doses) to remove clot using surgical aspiration followed with alteplase clot irrigation. The primary efficacy outcome was the adjusted dichotomized modified Rankin Scale (mRS) 0–3 vs 4–6 assessed at day 180 after symptom onset. Analysis was by intention to treat. (ClinicalTrials.gov number NCT00224770).

Findings—Between February 2, 2006 and April 8, 2013, 96 subjects were randomized and completed follow-up: 54 received treatment and 42 medical care. Primary safety outcomes: mortality, symptomatic bleeding, brain infections, as well as withdrawal of care, did not differ between groups. Asymptomatic hemorrhages were more common in the surgical group (3 (7%) vs. 12 (22%) p= 0.05) producing a difference of 15.1% (95% CI: 1.5% to 28.6%). The estimated absolute benefit, i.e., the unadjusted difference in observed proportions of all subjects with mRS 0–3 (33% vs 21%) at 180 days comparing MISPA vs. medical control, is 0.109 [95%CI: −0.088, 0.294; p=0.26], and is 0.162 [95%CI: 0.003, 0.323; p=0.05] after adjustment for potential imbalances in baseline severity between study arms (primary efficacy outcome).

Interpretation—MIS+rt-PA appears safe with an apparent advantage of better functional outcome at 180 days. Increased asymptomatic bleeding is a major cautionary finding. The MISTIE trial results, if replicable, could produce a meaningful functional benefit adding surgical management as a therapeutic strategy for ICH.

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Keywords

Intracerebral hemorrhage; Thrombolysis; rt-PA; Clot aspiration; Minimally Invasive Surgery; MISTIE

Introduction

Brain haemorrhage affects more than 5 million people each year.[1] It is the most severe form of stroke for which there is no evidence-based primary treatment.[2–4] Well executed pragmatic trials of therapy used in routine practice have not shown that any treatment substantially reduces haematoma size and brain tissue damage, and improves functional outcome. In the STICH (Surgical Treatment for Intracerebral Hemorrhage) I and II trials, routine craniotomy did not show an alteration of functional outcomes.[5,6] STICH I suggested clot removal may simplify and shorten overall medical care,[5] and STICH II demonstrated a non-significant 5.6% decrease in mortality. Nonsurgical trials of aggressive, early haemostasis,[7] showed some stabilisation of haematoma growth but no change in functional outcome. In the large INTERACT (Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial) II trial, early blood pressure (BP) lowering reduced clot growth by a small amount and led to a nonsignificant, 3.7%, gain in functional outcome.[8] The MISTIE II trial was designed to assess alteplase (Alteplase, Genentech, South San Francisco, CA, USA) dose response (stage one) and whether minimally invasive surgery (MIS) followed by thrombolytic treatment is safe and reduces, and perhaps reverses, the burden of clot on tissue (stage two)[9,10] and to provide preliminary functional outcome data.[10–15]

Methods

Study Design

MISTIE II was an international, multicenter (26 sites in the USA, Canada, UK, and Germany), randomized, phase 2 trial[16] of image-guided,[14] catheter-based[13] removal of ICH ≥20 mL, measured by the ABC/2 method.[17] All subjects were managed in an intensive care unit setting. Local institutional review board (or Ethics Committee) approval was obtained at each hospital.

Participants

Subjects with non-traumatic (spontaneous) ICH attributed to cerebral small vessel disease and not due to a macrovascular cause such as an aneurysm or AVM were candidates for this trial. After obtaining written, informed consent, all patients age 18–80 years old with spontaneous, non-traumatic, supratentorial ICH ≥20mL, Glasgow Coma Scale (GCS) score ≤14 or NIH Stroke Scale (NIHSS) score ≥6, a historical modified Rankin Scale (mRS) score of 0 or 1, whose ICH remained the same size for ≥ 6hrs and who satisfied all other inclusion/exclusion criteria listed in the Supplemental Appendix (page 4) were randomized.

Randomization and Blinding

Patients were randomized by local site personnel using a central web-based enrollment system. The trial statistician employed a randomly generated number sequence to allocate

patients to the surgical and medical groups. Patient allocation was stratified according to clot size with two schedules employed: one for ICH ≥20 mL and ≤40 mL; and one for ICH >40 mL as measured on the diagnostic CT. The trial had two pre-planned stages, which were managed by an independent data safety monitoring board (DSMB): a dose finding stage and a safety assessment stage. Stage one (dose finding) consisted of two doses (0.3mg and 1.0mg). A third dose, 3mg, was not investigated after a planned DSMB review. This decision decreased the sample size from 110 to 96 subjects. Subjects in stage 1 were randomized 3:1 to treatment (MIS plus the dose of rt-PA in that part) or medical management. In stage one only, blocks of 4 patients were employed within each randomization schedule to ensure a 3:1 assignment to treatment (MIS+rt-PA) versus control (medical management). After stage one enrollment and DSMB review were completed, a planned protocol amendment, occurred. This specified the use of alteplase at the selected 1 mg dose (based on safety profile and clot removal efficiency), use of a surgical oversight center (based on initial surgical performance) and addition of 365 day outcome assessments. This amendment was reviewed and approved by the DSMB and executive committee. Stage two remained stratified by size, used 1:1 randomization and evaluated the safety of treatment vs. medical management.

The first subject at every site was assigned to surgical management and served as a "credentialing subject" to document the surgeon's ability to perform the surgical protocol. Once a surgeon was credentialed, subsequent eligible patients were randomized to MIS+rt-PA or medical management (stage one: 3:1; stage two: 1:1). The assignments were not masked because of surgical assignment in the protocol. The number randomized in stage one was 29 to MIS+rt-PA and 17 to medical management; the corresponding numbers in stage two are 25 to MIS+rt-PA and 25 to medical management. Unlike stage one participants (followed up to 180 days), stage two participants were followed up for 365 days. The site examiners performing the outcome assessments were masked to treatment assignment.

Procedures

Stability Protocol

The risks of initial haematoma growth/instability were managed by use of a stability protocol combining normalization of coagulation parameters, BP management, and repeat computed tomography (CT) assessment of clot size, measured using the ABC/2 method. Six or more hours after the diagnostic CT, a stability CT was performed to ensure that the ICH clot had not expanded by >5 mL, providing image demonstration of a safe starting point for clot reduction therapy, defined as the absence of active bleeding before performing MIS+rt-PA. The CT could be repeated every six hours until the clot stabilized or just before the 48-hour eligibility window closed, whichever came first. In addition, a magnetic resonance image (MRI) or CT angiography (CTA) was required to rule out underlying pathology as the bleeding source; an angiogram was encouraged with equivocal findings on vascular pathology screening.[17] An INR ≤1.3, a normal aPTT, and BP stability were required prior to randomization.[18,19] After a protocol amendment, planned catheter insertion trajectories describing the skull entry site and the planned linear path to the hematoma target were shared by the site with the trial's Surgical Center for joint review (stage two only).

MIS Protocol

Individuals randomized to MIS+rt-PA were taken to the operating room and general anesthesia was induced. Image-guidance was used to place an introducer cannula within the middle two-thirds of the overall haematoma diameter, via a burr hole or twist drill opening. The introducer portion was then removed. Clot aspiration was performed using a 10 mL hand-held syringe until there was no longer any fluid component of the clot noted in the aspirate and/or until first resistance. A soft catheter was passed through a rigid, peel-away cannula into the residual haematoma, tunneled subcutaneously, and connected to a three-way stopcock and a closed drainage system. A postoperative CT was performed to confirm positioning of the soft catheter within, and stability of, the residual haematoma and catheter tract.

Thrombolysis Protocol

Three or more hours after catheter placement, intraclot rt-PA administrations of 0.3 mg in 1 mL or 1.0 mg in 1 mL were given every 8 hours, for up to 9 doses, or until a trial-defined surgical performance requirement was reached. All doses were followed by a 3 mL flush of preservative-free normal saline. After each assigned dose, the system was closed for 1 hour to allow drug-clot interaction, and then reopened to allow for gravitational drainage. Trial-defined surgical performance requirements were reduction of clot to either 20% of the volume measured on the stability CT prior to randomization, or to ≤ 15 mL, or occurrence of a clinically significant re-bleeding event, defined as a sustained drop of more than two points on the Glasgow Coma Scale (GCS) motor score with CT-demonstrated ICH enlargement. CT scans were subsequently obtained every 24 hours until dosing was complete to evaluate safety and drainage.

Medical Treatment Protocol

All subjects were managed using the American Heart Association recommendations for the treatment of non-traumatic (spontaneous) ICH.[18–19] This allowed for a standard approach to monitoring patients' airway, ventilation, intracranial pressure (ICP), sedation, and pharmacological treatment of intracranial mass effect. Patients randomized to receive standard medical care received follow up CT scans and other monitoring assessments on the same schedule as those randomized to receive MIS+rt-PA.

Follow-up

Subjects were followed with an MRI scan at Day 7. Subjects returned to clinic on Days 30, 180 (stages one and two), and 365 (stage two) and were contacted by phone at Days 90 (stages one and two) and 270 (stage two). A certified examiner assessed the modified Rankin Scale (mRS), Barthel Index (BI), Stroke Impact Scale (SIS), Glasgow Outcome Scale (GOS), extended GOS (eGOS), NIH Stroke Scale (NIHSS, clinic visits only) and a repeat CT (days 30 and 180 only).

Image analysis

To optimize accuracy and minimize investigator bias, clot volumes were analyzed by a core laboratory utilizing semi-automated segmentation and Hounsfield thresholds.[9] This was

performed using OsiriX software (version 4.1) on DICOM images of each subject's stability and treatment scans. This approach has been validated for accuracy and inter-rater reliability.[20] The core lab values were utilized in all analyses. Core lab defined location as either lobar or deep (putamen or thalamus).

Primary and Secondary Outcomes

The aim of the MIS+rt-PA treatment was to achieve near total clot dissolution without procedure-related safety events that would endanger the lives of the patients beyond the risks associated with intensive medical treatment. The primary safety outcomes were 30-day mortality, 7-day procedure-related mortality, 30-day bacterial brain infection, and symptomatic bleeding within 72-hour after the last dose. The primary efficacy outcome was the adjusted 180-day dichotomized (mRS 0–3 vs. 4–6.) expressed as the proportion of all mRS subjects ≤3.

Secondary efficacy outcomes were 180-day ordinal mRS, 365-day ordinal mRS, and difference in clot-size reduction at the end of the treatment for each group. All adverse and serious adverse events were reported during the acute treatment period and all serious adverse events until the end of the follow-up.

Statistical analysis

Analyses are presented at three levels: primary planned safety analysis, primary intention to treat efficacy analysis, and exploratory analyses. The latter two are adjusted analyses.[16]

Target Sample Size

The study was designed and powered to explore safety and dosing for MIS+rt-PA. It was not powered to observe effect of treatment on functional outcome. This study had 90% power to detect a doubling in the rate of any rebleeding from 8% to 16% between dose groups of 15 subjects who received the MIS+rt-PA intervention at each dose level. The study had 80% power to detect a difference in rates of clot dissolution of 3% per day or greater, between groups of 15 subjects on different doses of rt-PA (stage one). It had a 91% to 99% power to observe one or more symptomatic bleeds for 15 subjects if the true bleeding rate was 15%. For stages one and two combined, assuming a total of 80 subjects, it had from 52% to 62% power to detect an absolute difference of 25% in the mortality rate assuming a 50% mortality rate. The target sample size for stage one was 20 subjects per dose group and for stages one and two combined the final target sample size was a total of 96 subjects.

Safety Analysis

Analyses tested the hypothesis that there was no difference between the treatments being compared. We defined and pre-specified thresholds for the safe use of MIS+rt-PA for the treatment of ICH relative to standard medical care: for 30-day mortality (70%), symptomatic brain bleeding (35%), and bacterial brain infection (15%). We tested rates of events across groups by Fisher's exact test and calculated exact binomial 95% confidence intervals (CI) for the rate of events. The method of Kaplan and Meier was used to estimate the survival functions (with 95% CI) for patients in both groups.

Intention-to-Treat Efficacy Analysis

We estimated the mean benefit of MISTIE treatment vs. medical control using the ITT principle. Specifically, we estimated the difference between the probability of having 180-day mRS ≤3, referred to as a good outcome, under treatment vs. control. This average treatment effect was estimated using a simple difference in proportions among those with observed 180-day outcomes (unadjusted estimator) and also using an estimator that adjusts (adjusted estimator) for missing outcome data using the double-robust methodology for censored data of Rotnitzky *et al.*[21,22] The adjusted estimator is fully described in the appendix (page 10); it has greater precision than the unadjusted estimator because of adjustments for potential imbalances between study arms in the prognostic baseline covariates: NIHSS, GCS, ICH volume, and intraventricular haemorrhage (IVH) volume.[21]

Exploratory Analyses

Patient characteristics, safety, and outcome measures were reported by each site. To describe medical events we utilized terms and definitions from the Medical Dictionary for Regulatory Activities (MedDRA) and centrally adjudicated. Longitudinal plots were used to depict the percent ICH clot reduction from stability over time for each participant. LOESS (locally weighted scatter-plot smoothing) was applied to calculate mean clot reduction over time by treatment group.[23]

To investigate the role of clot volume reduction by MIS+rt-PA on outcome, we used logistic regression models to estimate the association between the primary outcome measure of dichotomized 180-day modified Rankin Scores ≤3 with treatment group, clot removal, and the baseline variables identified in the study protocol[24]: ICH clot size at randomisation, age, enrollment NIHSS, presence of IVH, and location of ICH. The multivariable logistic regression models were created by first considering univariable analyses to determine the independent associations between each covariate and the outcome. For parsimony, the variables chosen for the multivariable regression analyses, in addition to treatment, were those with $p<0.1$ in the univariable analyses; these variables are similar to those from previous ICH studies.[6,8,25] Other prespecified baseline variables that were non-significant in the univariate analyses were systematically considered as candidate explanatory variables in the multivariate analysis, for the purpose of hypothesis generation. As in any variable selection method for model building, our approach has limitations and should be regarded as exploratory; see Sauerbrei et al.[26] for a discussion of model building approaches. Sensitivity analyses were performed that considered all possible ‘good’ and ‘bad’ outcomes for patients with missing 180-day mRS scores to determine a possible tipping point that would change the statistical association between the outcome and clot removal.[27,28] Logistic regression was used for sensitivity analyses of subgroups.

Surgical Removal

To manage the influence of time on the subjects, we defined volume of clot removed at the specific times defined as follows: for patients in the MIS+rt-PA arm, the end of treatment (EOT) was defined to be 24 hours after the last dose of rt-PA was administered; the EOT scan for patients in the medical management arm was defined as the scan closest to the

median EOT scan time for the surgical patients (4 days post randomization).[9] The EOT scan among patients who received delayed craniotomy in the medical management arm was defined, on an ITT basis, as the scan prior to craniotomy. All analyses were performed using the statistical packages STATA (version 12.0) and R (version 3.2). The trial was registered on clinicaltrials.gov (NCT00224770).

Role of the funding source

The NIH/NINDS provided input regarding the study design during the grant review process and the NIH/NINDS-appointed DSMB provided the same during active recruitment. The NIH/NINDS-appointed DSMB and Genentech, Inc. approved the decision to submit the paper for publication. DFH had full access to all study data and had final responsibility for the decision to submit for publication.

Results

The trial ended after target enrollment was achieved. Study enrollment for stage one took place from February 2, 2006 to August 2, 2009. (See Fig.1). Stage two enrollments took place from December 21, 2009 through April 3, 2012, with the final follow-up visit occurring on April 8, 2013 after approval of the planned protocol amendment. The demographic characteristics of the randomized subjects are shown in Table 1. Fifty-four subjects (stages one and two combined) were randomized to the intervention: eight (15%) achieved the surgical goal at the end of the surgical procedure (i.e., after aspiration and catheter placement, and 46 (85%) received rt-PA via the catheter to further reduce the haematoma size (MIS+rt-PA). Forty-two subjects (stages one and two combined plus 6 subjects from stage one endoscopy arm) were randomized to medical care. Delayed deterioration led to craniotomy in four medical and in two MIS+rt-PA subjects (post MIS procedure). Overall, event rates were below pre-specified safety thresholds and the primary safety profile of symptomatic events was similar for both groups (Table 2). The entire surgical group had non-significantly more asymptomatic and significantly more total bleeding (Table 2). Kaplan-Meier analysis of survival over 365 days demonstrated no adverse effect of MIS+rt-PA on survival (hazard ratio 1.32 (95% CI: 0.618, 2.82) log rank p=0.473); see Figure S1 on page 13 in the Supplementary Appendix). Those randomized to the treatment arm achieved more rapid ICH volume reduction when compared to the standard medical care group (Fig. 2). Thirty-one of thirty-five neurosurgeons easily acquired the technical skills (87% training efficiency). There were no differences in volume of clot removed between a surgeon's 1st and 4th procedure performed or between "neophyte" and "expert" surgeon (data not shown).

Both rt-PA doses increased clot removal, when compared to the control group, with no differences in symptomatic bleeding rate 0 (0%) vs. 2 (13%) for 1.0. mg vs 0.3 mg, respectively and 1 (2%) for control (difference between doses 95% CI: −3.87%, 30.54%; p=0.483); leading to the selection of the 1.0 mg dose for stage two (Table S6, appendix page 22). Overall, for both stages one and two symptomatic bleeding was 1 (2%) vs. 5 (9%); difference between treatment groups 6.9% (95%CI: 4.6%, 18.1%; p=0.2263). Reduction of clot volume over time and for the ITT analysis at about Day 4 is shown in Figure 2. Overall,

the mean (SD) percent reduction of haematoma size (EOT ICH/Randomization ICH) in the MIS+rt-PA group was 57% (± 25%). The mean (SD) EOT ICH was 20 (± 14) mL in the MIS+rt-PA subjects and 41 (± 15) mL p< 0.0001 in the medical management subjects (mean [95% CI] difference: 21 [15mL, 27 mL]).

Results: ITT Efficacy Analysis

The primary efficacy outcome was the proportion of all subjects with mRS ≤3 at 180 days was 21% for medical and 33% for MIS arms. The unadjusted estimate of the absolute benefit (i.e., the difference between the probability of having 180 day mRS ≤ 3 under treatment vs. control) is 0.109 [95%CI: −0.088, 0.294], based on the n=96 ITT randomized participants. The adjusted estimate using the robust method of Rotnitzky *et al.*[21,22] is an absolute benefit of 0.162 [95%CI: 0.003, 0.323].

A secondary outcome was mRS ≤3 at 365 days which was only measured for stage two participants (n=56, who had extended follow-up). The unadjusted estimate of the absolute benefit at 365 days is 0.117 [95%CI: −0.146, 0.370] and the adjusted estimate was and 0.115 [95%CI: −0.171, 0.306].

Additional secondary analyses focus on ordinal (rather than dichotomous) mRS scores. The proportion in each mRS category at 180 days (stages one and two participants) and at 365 days (stage two participants only) is shown in Table 3 demonstrating the beneficial trend is maintained at the later time frame.

Results: Exploratory Analyses

Results of the logistic regression analysis on the binary indicator good vs. unfavorable mRS scores are presented in Table S1 on page 17 of the Supplementary Appendix. When we considered univariable (unadjusted) models, we found that pre-randomized ICH volume, age, enrollment NIHSS, the presence of any pre-randomization IVH, and the absolute clot volume remaining at the EOT were statistically significant; assignment to MIS+rt-PA resulted in a nonsignificant benefit (similar to the estimates in the ITT efficacy analysis above). Table S1 shows the results of the multivariable logistic regression of good 180-day outcome on the aforementioned variables. After controlling for age, enrollment NIHSS, pre-randomized ICH volume and presence of IVH, and assignment to MIS+rt-PA, the absolute volume of clot remaining at the EOT is statistically significant. Specifically, the model predicts that with all other variables held constant, each 10 mL of additional clot remaining at the end of treatment is associated with a relative reduction in the odds of a good 180-day outcome by almost 50% (Adjusted Odds Ratio 0.496; [95%CI] 0.259, 0.949, p= 0.034). This is consistent with the hypothesis that clot volume reduction is an important mechanism through which assignment to MIS+rt-PA results in greater probability of mRS ≤3 at 180 days. Unadjusted ITT analyses in different subgroups are shown in Figure S2 on page14 of the Supplementary Appendix. There were no statistically significant results by subgroup, but all point estimates are in the beneficial direction of the MIS+rt-PA treatment compared to medical management and the point estimate for deep clot location corresponds to greater benefit than for lobar clot location, although again not statistically significant.

Discussion

MIS+rt-PA appears safe when tested in our phase 2 study, with a possible advantage of better functional outcome at 180 days. However, increased asymptomatic bleeding is a major cautionary finding. MISTIE II is an important test of a very gentle approach to ICH evacuation, minimizing potential tissue injury inherent in craniotomy. It employs image guidance and a novel combination of surgery and drug treatment. The MISTIE II approach was reliably reproduced by surgeons new to the treatment concept but trained in the general principles. The surgical technique is a simple and logical extension of routine image guidance and intracerebral catheter placement. Where both pragmatic (craniotomy) and simple translational (factor VIIa) approaches have failed in trials, our results are promising and contrary to the belief that surgical manipulations to remove blood may damage brain tissue and impair long-term function.[5,29,30] Because supportive medical care is the only universally-accepted ICH treatment, these results are promising[19,30] and consistent with trends from studies of convenience samples or at single sites.[31,32] We have demonstrated that MIS can be performed safely at multiple sites, that rt-PA can be combined with MIS safely, and that the MISTIE treatment, though different from current practice, can be adopted without difficulty at interested sites. Thus, MISTIE could be a promising approach to a worldwide health problem. If the apparent benefits of the MISTIE approach are replicable, the findings could lead to a change in treatment of ICH.

Several limitations are considered. This trial size is small and screening yield low (123 enrolled of 4103 screened). It was powered to observe relatively high safety thresholds (15% bleeding), not efficacy; thus, the range of estimated benefit in the ITT analysis is wide and the true benefit could be different. However, all known baseline severity factors (ICH size, IVH size, age, NIHSS, GCS and stability) were nearly balanced between arms. The point estimates in both adjusted ITT analyses are suggestive of a treatment benefit. Safety conclusions are similarly limited by sample size; the substantial difference in asymptomatic bleeding demonstrates that combining MIS and alteplase still has important risks.

We hypothesize that the effect of the MISTIE treatment on mRS outcome is mediated through clot volume reduction, although such a relationship cannot be assessed without a second trial. We considered potential confounders of the relation between clot-reduction and mRS outcomes, such as length of ICU care and use of ICP monitoring; these were similar in both treatment groups. Surgical bias could unknowingly account for good outcomes; however, the usual source of this problem—selection of less severe subjects for surgery—did not occur, as the randomized surgical subjects were slightly, but non-significantly, more impaired at baseline, and all subjects were consented without knowledge of surgical allocation, further limiting the possibility of surgical selection bias. A bias could also be that the population was not fully representative of the general population of ICH subjects and that the routine care that medical management subjects received may account for the surgical benefit by having selected a sicker subgroup. This is not likely, as the distribution of good and poor outcomes for the medical subjects is similar to that found in observations of other ICH populations. A bias in the amount of rehabilitation care a particular group received is also possible. Finally it remains possible that specialized skills, such as surgical skill or superior stroke center organizational resources produced the benefits rather than the MISTIE

treatment, rendering the results not reproducible by a wider set of surgeons or centers. This seems unlikely, as the majority of the surgeons, although trained in image guidance and catheter placement, previously had not combined these skills to treat ICH. Similarly, attention to BP control in MISTIE is already a well-developed and standard approach in established stroke center protocols.[8,18,23,25,33]

Our outcome data suggest that MIS+rt-PA has the potential to be efficacious where routine craniotomy has failed. Comparisons to existing trial data[31] and meta-analysis data[32,34,35] are reassuring for the possible generalizability of these findings. Mortality was low and not different for medical or surgical subjects and was similar to STICH I & II mortalities,[36,37] suggesting that the surgical procedure itself is low risk. This is in agreement with other MIS observations.[32] The low mortality may relate to the infrequent discontinuation of care. Interestingly, the deep ICHs that responded so poorly to invasive craniotomy in STICH I appear to have benefitted from MIS plus rt-PA.

Administration of rt-PA following MIS also appears safe in this small sample utilizing mortality and symptomatic bleeding as the main safety measures, but only if performed under MISTIE protocol conditions. Some rebleeding must be expected in ICH patients and with exposure to surgery and thrombolytic drug. The significantly increased occurrence of asymptomatic bleeding provides biologic plausibility for further safety evaluations. The combined use of imaging to define clot stability and BP control appears to have limited the frequency of symptomatic bleeding events in both arms of MISTIE and the absence of a symptomatic rebleeding difference between MIS+rt-PA and controls is a reassuring safety profile for a thrombolytic treatment approach; external monitoring and core imaging lab assessments for enlargement reinforce our confidence in this safety profile. However, the presence of higher frequencies for all bleeding categories in the treatment arm demonstrates that the possible benefits of MIS+rt-PA come with a clear potential bleeding risk that must be managed with clinical vigilance. A larger sample is needed to confirm that the current clinical vigilance (ICH stability, dose and BP control) is reproducible in the widest possible population. A phase 3 study would provide a better estimate of safety and particularly bleeding events.

The MISTIE approach targets two major sources of ICH morbidity: mass effect and inflammation. The functional outcomes in the treatment group are consistent with better tissue preservation[9,10] and, when compared to the medical management group equally treated with ICH stabilization and BP control, reassuring for the potential to reproduce the result in other populations. The trial design was not able to differentiate whether better tissue preservation was attributable to mass-effect reduction or to removal of inflammation-provoking blood products; most likely both are important effects of clot reduction. Because removal took place over three to four days, it is likely that some degree of secondary injury from mass effect and inflammation occurs over days, not hours. If the MISTIE approach of minimal mechanical manipulation is to be employed the majority of subjects (85%) will require rt-PA irrigation to achieve large reductions of clot volume. Analysis of subgroups suggests the potential for benefit in a window of at least 48 hours. If the time window is this large, then MISTIE treatment could possibly be scheduled urgently rather than in an emergent manner. The model and subgroup findings represent hypothesis generating

information such as time dependence of treatment and require independent confirmation. For example if much damage occurs by chemical means in the initial hours there could be additional benefit to very early removal or biochemical blockade of such events.

Testing the reproducibility of our results will require at least 500 subjects in a randomized trial; possibly more, if the estimate of therapeutic effect is falsely large or if the symptomatic bleeding risk is underestimated. A rigorous test should include stringent reproduction of the standard elements of the surgical and drug-administration tasks used in MISTIE II in a cohort of subjects recruited from the widest possible set of stroke hospitals utilizing image guidance, CT imaging, and BP control to treat ICH. Decreases (s) in treatment related bleeding events might benefit outcome. Testing generalisability will provide a better estimate of the number of treatment candidates. Safety and preliminary outcome data indicate that MIS+rt-PA is a realistic approach to ICH, possibly improving long-term function and the ability to live at home, and perhaps, decreasing cost, even for patients with large ICH volumes.

Panel: Research in Context

Evidence before this study

Minimally invasive surgery was reviewed in a recent meta-analysis by Zhou et al. This review of international databases, websites, and conference summaries such as Pubmed and the International Clinical Trials Registry were searched through December 2011 using the following key words: intracerebral, intracranial, cerebral, brain, putaminal, intraparenchymal, basal ganglia hemorrhage, thalamic, hemorrhagic stroke, hemorrhage, hematoma, minimally invasive, minimal surgical procedures, endoscopy, stereotaxy(ic), aspiration, keyhole, or craniopuncture. Inclusion criteria were nontraumatic (spontaneous) ICH diagnosed on a CT and randomized controlled trials with minimally invasive surgery compared to a control group. Exclusion criteria were traumatic brain injuries, infratentorial ICH, and studies with quality assessments less than 2 on the Cochrane criteria scale. An Egger test was conducted to check for publication bias for primary and secondary outcomes (P=0.377 and P=0.805 respectively).

We have thirty years of evidence that clinical injury from ICH is directly related to the size of the clot. Benefit from the obvious solution of reducing the clot size by mechanical means has been difficult to demonstrate. Now with the completion of STICH 1 & 2, we have a strong indication that pragmatic use of open craniotomy does not produce the presumed benefits. Today, when caring for the millions of spontaneous ICHs that occur yearly, clinicians are faced with substantial class 1 evidence demonstrating no effect of routine craniotomy on the functional performance of subjects experiencing brain hemorrhage. STICH 1 also demonstrated that subjects with deep basal ganglia hematomas were particularly likely to experience a poor outcome, if they underwent craniotomy. These findings were consistent with samples from the general population and suggest, in a congruent manner, that an alternate approach to ICH be considered. Small studies have tested the idea that catheter-based, minimally invasive clot volume reduction can be performed without loss of life and that individual subjects experience improved outcome in increased proportion. Because of the significant morbidity and mortality associated with

ICH, hyper acute craniotomy and deep location of ICH in particular, we chose to organize a two-stage test of the possibility that minimally invasive surgery, performed on stabilized subjects provides benefit from clot reduction without exposing patients to as much injury as was possibly occurring from open craniotomy. Further testing of this idea could include studies of the recovery process as well as larger trials.

Added value of this study

To the best of our knowledge MISTIE II is the first rigorous study of brain MIS because it was a multisite study with a standardized surgical task designed to eliminate cortical incision, electrocautery, toxic exposure to thrombin and the attendant additional loss of deep brain tissue. The results provide evidence of safety of the MIS approach and identify the best dose of thrombolytic to be employed for clot volume reduction. It identifies that you cannot combine MIS and alteplase without increased incidence of asymptomatic bleeding. The need for meticulous management of bleeding risk is inherent in this finding. In addition, results produced an estimate of treatment effect that is substantial (>10% absolute benefit) and longstanding (one year). As such, these data provide novel safety, surgical performance and overall proof of concept for the hypothesis that MIS has robust potential as a unique intervention for intracerebral hemorrhage.

Implications of all the available evidence

Although this manuscript focuses on the results of MISTIE II and the possible role of clot volume reduction as a mechanism of treatment, it is consistent, in a clearly defined prospective manner, with the external data from single site and meta-analysis of convenience samples. The data provide a sound basis to estimate a treatment effect and inform clinical goals for the surgical task of clot size reduction, if performed in the standard manner described (i.e., single tissue trajectory, small tissue cannula, minimal mechanical manipulation). The manuscript highlights the possibility that MIS is a technique with promise to mechanically reduce lesion size in all or many subjects and has the potential to directly alter the course of events set in motion by the presence of blood clot within brain tissue and treat a disease for which we have no therapy. Trials utilizing this approach will require well-defined management of bleeding risk and identification of relevance or not to amyloid vasculopathy. The time window for ICH trials remains broad as sub group analysis in MISTIE did not find benefit or detriment in the times observed. The precise role of clinical stability in patient selection is another subject for future trials. The findings have stimulated multiple smaller tests of parts of our MIS thought process with many variations of equipment and surgical technique. Sharing the full results of MISTIE II is likely to stimulate further investigations of a worldwide problem that is serious and growing. An investigator-initiated, publically sponsored NIH trial MISTIE 3 is underway to prospectively test the generalizability of the MISTIE 2 surgical task and medical stabilization protocol.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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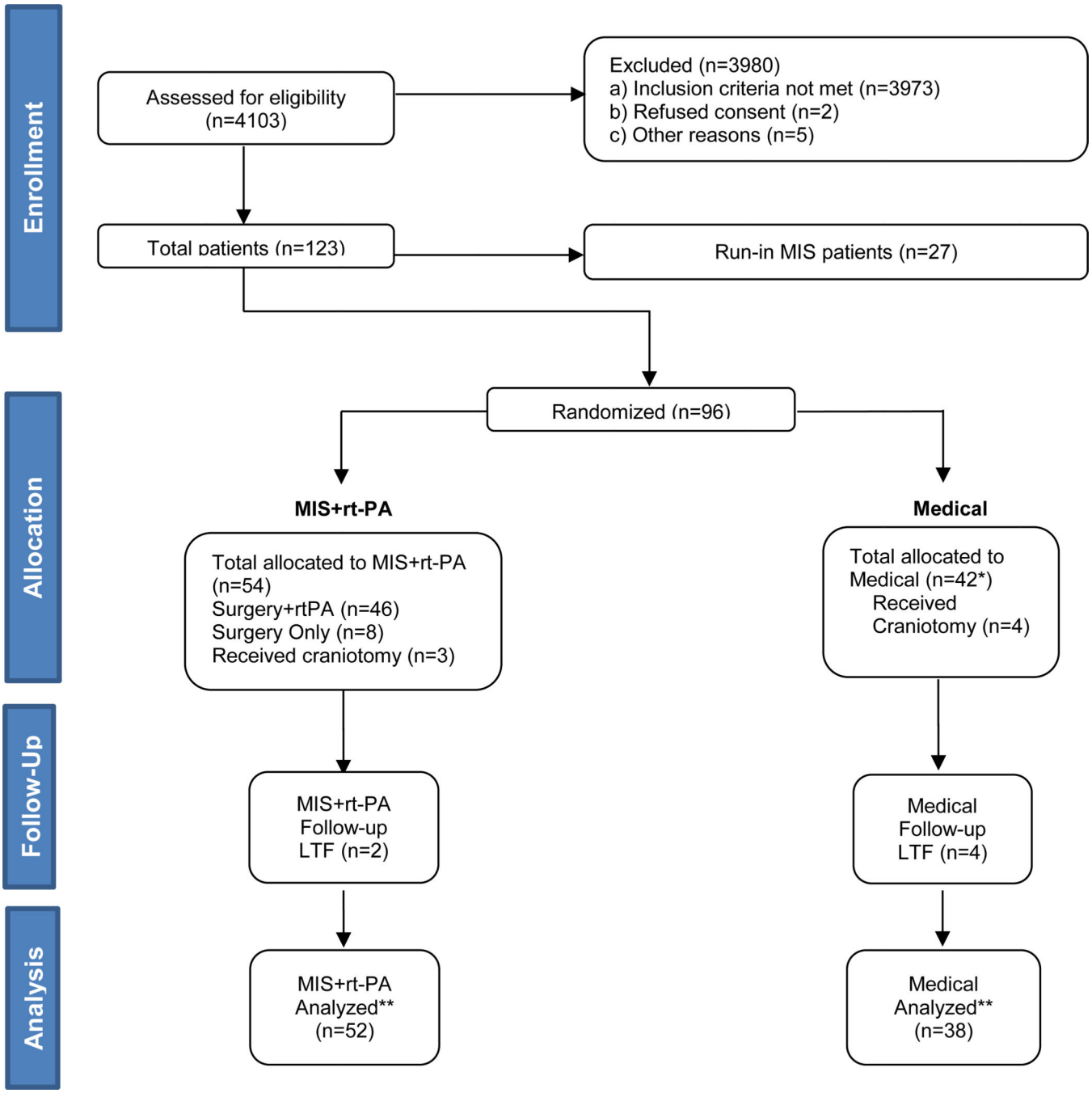

Figure 1. CONSORT diagram of the MISTIE II trial

*includes 6 medical subjects from Tier III (not shown); **ITT efficacy analysis

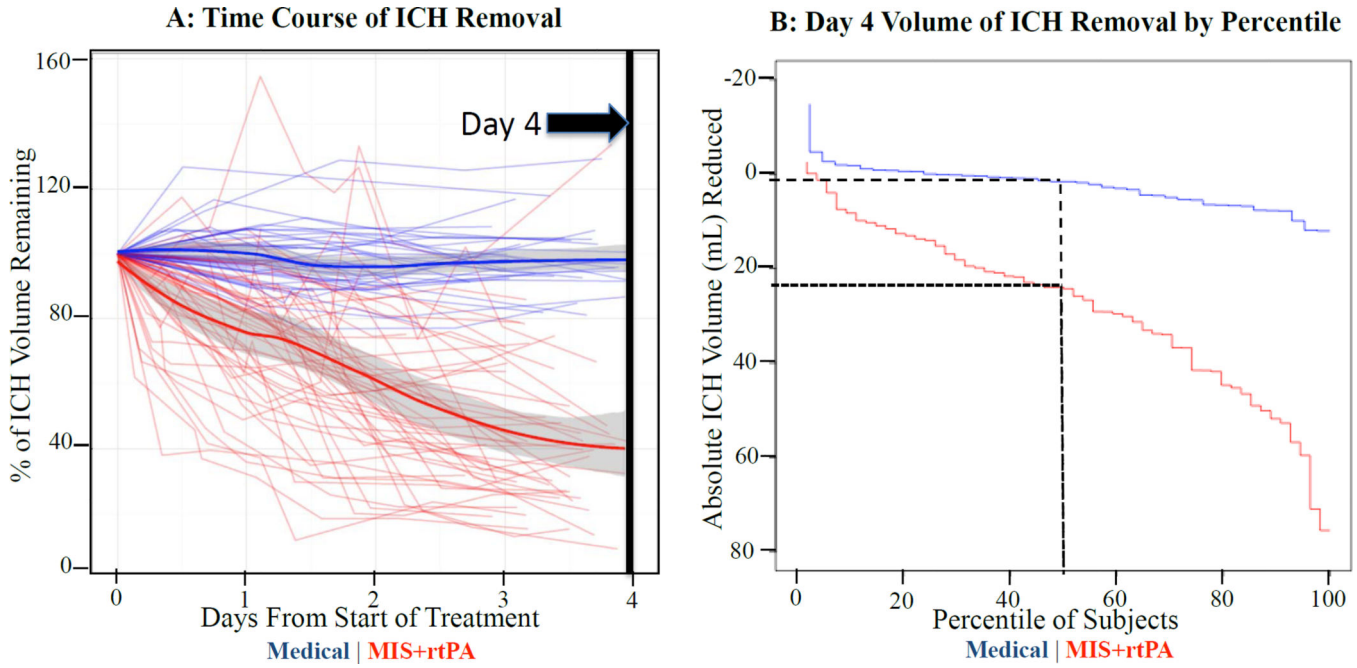

Figure 2. ICH removal by treatment group

This figure demonstrates the treatment effectiveness measured in terms of amount and timing of ICH removal. Panel A is a plot of percent of clot remaining as measured on daily CT scan after achieving clot size stability and initiating MIS+rt-PA, thin lines are individual subjects. Dense blue and red lines are the fitted average response. The gray-shaded area is the 95% confidence intervals of this average response. The black line identifies the average occurrence of the 24-hour post last treatment time point. Panel B represents the distribution of each subject's clot removal expressed as absolute volume reduction on the day 4 EOT CT scan. The dashed line indicates the 50th percentile subject and respective ICH volume reduction for the medical subject cohort. The dotted line indicates the 50th percentile subject and respective volume reduction for this subject in the MIS+rt-PA group. All volumes were detrmined by the core lab. Removal is as defined in the methods.

Table 1

Baseline Demographics and Characteristics by Treatment Group.*

	Medical (N=42)	MIS+rt-PA (N=54)	P values
Demographic variables			
Age in Years: Mean (SD)	61.1 (12.3)	60.7 (11)	
Age in Years: Median (IQR)	62 (49.5 - 73)	60 (54 - 69)	
Gender: Male	28 (66.7%)	35 (64.8%)	
Race			
Caucasian	23 (54.8%)	30 (55.6%)	
African American	11 (26.2%)	18 (33.3%)	
Hispanic	5 (11.9%)	4 (7.4%)	
Other	3 (7.1%)	2 (3.7%)	
Baseline variables			
Diabetes	11 (26.2%)	14 (25.9%)	
History of Hypertension	34 (81%)	49 (90.7%)	
Other Cardiovascular Disease	14 (33.3%)	22 (40.7%)	
Alcohol Abuse	7 (16.7%)	17 (31.5%)	
Presentation Blood Pressure			
Systolic BP (mmHg): Mean (SD)	186.7 (34.1)	186.4 (33.0)	
Diastolic BP (mmHg): Mean (SD)	101.9 (20.4)	106.8 (27.7)	
Enrollment GCS			
3–8	13 (31%)	17 (31.5%)	
9–12	12 (28.6%)	20 (37%)	
13–15	17 (40.5%)	17 (31.5%)	
Enrollment NIHSS: Mean (SD)	21.6 (8.9)	22.8 (8.5)	
Enrollment NIHSS: Median (IQR)	21 (17 - 27)	22 (18 - 29)	
Stability CT (last CT prior to enrollment)			
ICH Volume (mL): Mean (SD)	43.1 (15.3)	48.2 (19.6)	
ICH Volume (mL): Median (IQR)	41.4 (33.2 - 50)	43.4 (31.6 - 59.3)	
IVH Volume (mL): Mean (SD)	2.4 (3.9)	4.6 (7.7)	
IVH Volume (mL): Median (IQR)	0.7 (0 - 3.1)	0.8 (0 - 4.4)	
Clot Location			
Lobar	15 (35.7%)	18 (33.3%)	
Deep	27 (64.3%)	36 (66.7%)	
Treatment variables			
% With ICP monitoring	10 (23.8%)	9 (16.7%)	0.444

	Medical (N=42)	MIS+rt-PA (N=54)	P values
% Ventilated	16 (38.1%)	25 (46.3%)	0.533
Time from Ictus to Randomization (Days)	1.3 (0.6)	1.2 (0.5)	0.174
Systolic BP (mmHg): Mean (SD)	145.3 (20.7)	143.9 (21.1)	0.741
Diastolic BP (mmHg): Mean (SD)	73 (14.9)	71.2 (13.1)	0.534
Time from Randomization to Surgery (Hours)		6.6 (7.8)	
Surgery (elapsed time from symptom onset)			
≤ 36 Hours		31 (57.4%)	
> 36 Hours		23 (42.6%)	
Number of Doses of rt-PA: Median (IQR)		3.5 (2 - 5.8)	
Days in ICU (IQR)[†]	8 (5–13)	8 (6–15)	0.839
Days to return home (IQR)[‡]	89 (54–146)	51 (36–89)	0.031

[*] SD, Standard deviation; IQR, inter-quartile range. Unless otherwise specified, the values are expressed as count and % within group.

[†] P=0.839 comparing medical to MIS+rt-PA.

[‡] P=0.031 comparing medical to MIS+rt-PA

Table 2

Adjudicated Safety Events, with Thresholds for Randomized Medical and MIS+rt-PA with 95%CI.

Event	Study-stop threshold	Medical (N=42)		MIS+rt-PA (N=54)		p-value
		no (%)	95% CI	no (%)	95% CI	
Died within 0–7 days	10%	0 (0%)	(0%, 8.4%)	1 (1.9%)	(0.1%, 9.9%)	0.562
Died Within 0–30 Days	70%	4 (9.5%)	(2.7%, 22.6%)	8 (14.8%)	(6.6%, 27.1%)	0.542
Bacterial Brain Infection 0–30 Days *	15%	1 (2.4%)	(0.1%, 12.6%)	0 (0%)	(0%, 6.6%)	0.438
Symptomatic Bleed 72 h post last dose †	35%	1 (2.4%)	(0.1%, 12.6%)	5 (9.3%)	(3.1%, 20.3%)	0.226
Asymptomatic Bleed 72 h post last dose ‡	n/a	3 (7.1%)	(1.5%, 19.5%)	12 (22.2%)	(12%, 35.6%)	0.051
Symptomatic or Asymptomatic Bleed 72 h post last dose §	n/a	4 (9.5%)	(2.7%, 22.6%)	15 (27.8%)	(16.4%, 41.6%)	0.038

* Bacterial brain infection criteria included cultured organism identification in the presence of fever, relevant lab values, and associated clinical symptoms.

† Symptomatic bleeding criteria included radiographic evidence of an increase in clot volume (>5ml increase) associated with a decrease in the GCS motor scale score of more than two points sustained for a minimum of eight hours or associated clinical symptoms in the opinion of the site investigator.

‡ Asymptomatic brain bleeding was reported and adjudicated to include those events where clot size increase (>5ml increase) was confirmed by the core lab on volumetric measurement of the CT scan by comparison to the most previous CT scan, but where no alteration of GCS was noted.

§ Symptomatic or asymptomatic bleed is the total of all adjudicated bleeding events.

Table 3

Functional Outcome Showing Modified Rankin Scale Scores at Days 180 and 365 Comparing MISTIE Treatment vs. Medical Controls for All Randomized subjects.

	Treatment Group Day 180*		Treatment Group Day 365**	
mRS Score	**Medical (N=42)**	**MIS+rt-PA (N=54)**	**Medical (N=31)**	**MIS+rt-PA (N=25)**
0	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)
1	0 (0.0%)	1 (1.9%)	1 (3.2%)	3 (12.0%)
2	4 (9.5%)	6 (11.1%)	2 (6.5%)	2 (8.0%)
3	5 (11.9%)	11 (20.4%)	3 (9.7%)	2 (8.0%)
4	12 (28.6%)	13 (24.1%)	6 (19.4%)	3 (12.0%)
5	6 (14.3%)	7 (13.0%)	3 (9.7%)	2 (8.0%)
6	11 (26.2%)	14 (25.9%)	11 (35.5%)	10 (40.0%)
Missing	4 (9.5%)	2 (3.7%)	5 (16.1%)	2 (8.0%)

*Includes participants from primary analysis set (which includes randomized patients from stages one and two). For graphical display see Supplement Figure S4.

**Includes only randomized participants enrolled in stage two, i.e., those enrolled after protocol change extending follow-up to 365 days.