Intravenous glibenclamide for cerebral oedema after large hemispheric stroke (CHARM): a phase 3, double-blind, placebo-controlled, randomised trial

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Summary

Background No treatment is available to prevent brain oedema, which can occur after a large hemispheric infarction. Glibenclamide has previously been shown to improve functional outcome and reduce neurological or oedema-related death in patients younger than 70 years who were at risk of brain oedema after an acute ischaemic stroke. We aimed to assess whether intravenous glibenclamide could improve functional outcome at 90 days in patients with large hemispheric infarction.

Methods CHARM was a phase 3, double-blind, placebo-controlled, randomised trial conducted across 143 acute stroke centres in 21 countries. We included patients aged 18–85 years with a large stroke, defined either by an Alberta Stroke Program Early CT Score (ASPECTS) of 1–5 or by an ischaemic core lesion volume of 80–300 mL on CT perfusion or MRI diffusion-weighted imaging. Patients were randomly assigned in a 1:1 ratio to either intravenous glibenclamide (8·6 mg over 72 h) or placebo. The study drug was started within 10 h of stroke onset. The primary efficacy outcome was the shift in the distribution of scores on the modified Rankin Scale at day 90, as a measure of functional outcome. The primary efficacy outcome was analysed in a modified intention-to-treat population, which included all randomly assigned patients aged 18–70 years. The safety population comprised all randomly assigned patients who received a dose. This trial is registered with ClinicalTrials.gov (NCT02864953). The trial was stopped early by the sponsor for strategic and operational reasons (slow enrolment because of COVID-19), before any unblinding or knowledge of the trial results.

Findings Between Aug 29, 2018, and May 23, 2023, 535 patients were enrolled and randomly assigned, of whom 518 received a dose (safety population) and 431 were aged 18–70 years and comprised the modified intention-to-treat population (217 were assigned glibenclamide and 214 placebo). The mean age of patients was 58·7 (SD 9·0) years in the placebo group and 58·0 (9·5) years in the glibenclamide group; the median US National Institutes of Health Stroke Scale (NIHSS) score was 19 (IQR 16–23) in the placebo group and 19 (IQR 16–22) in the glibenclamide group; and the mean time from stroke onset to study drug start was 8·9 h (SD 2·1) in the placebo group and 9·2 h (2·1) in the glibenclamide group. Intravenous glibenclamide was not associated with a favourable shift in the modified Rankin scale at 90 days (common odds ratio [OR] 1·17 [95% CI 0·80–1·71], p=0·42). 90-day mortality was 29% (61 of 214) in the placebo group and 32% (70 of 217) in the glibenclamide group (hazard ratio 1·20 [0·85–1·70]; p=0·30). Serious adverse events in the prespecified safety population were consistent with the known safety profile of glibenclamide and included hypoglycaemia in 15 (6%) of 259 patients in the glibenclamide group and in four (2%) of 259 patients in the placebo group, leading to dose interruption or reduction in seven (3%) patients in the glibenclamide group and in one (<1%) in the placebo group.

Interpretation Intravenous glibenclamide did not improve functional outcome in patients aged 18–70 years after large hemispheric infarction, although the trial was underpowered to make definitive conclusions because it was stopped early. Future prospective evaluation could be warranted to identify a possible benefit of intravenous glibenclamide in specific subgroups.

Funding Biogen.

Introduction

In 2021, stroke was the third leading cause of death and fourth leading cause of disability-adjusted life-years worldwide, with ischaemic stroke comprising just under a third of incident strokes.[1] Large hemispheric infarction is a severe form of ischaemic stroke that involves the majority of the middle cerebral artery territory. Cerebral oedema can develop as a complication of large

Lancet Neurol 2024; 23: 1205–13

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed for randomised controlled trials published in English between Jan 1, 2000, and Aug 1, 2024, using the search terms "ischemic stroke" AND "brain edema" AND "intravenous glyburide" or "intravenous glibenclamide". We found two prospective clinical trials evaluating intravenous glibenclamide for acute ischaemic stroke. A pilot trial in patients with large hemispheric infarction showed the initial feasibility of enrolling and treating a critically ill stroke population. This study did not have a control group and was not blinded. One randomised double-blind trial evaluated participants with large hemispheric infarction. This trial did not meet the composite primary endpoint (avoidance of decompressive craniectomy and improved functional outcome). However, the secondary analysis suggested possible efficacy of glibenclamide for improving functional outcome in patients younger than 70 years.

Added value of this study

The CHARM trial is, to the best of our knowledge, the first phase 3, double-blind, placebo-controlled randomised trial to evaluate the efficacy of intravenous glibenclamide administered within 10 h of stroke onset for the prevention of brain oedema and improvement in functional outcome. The trial was large—conducted across 21 countries—and was the first to include patients with acute ischaemic stroke and large hemispheric infarction undergoing endovascular reperfusion treatment for large vessel occlusion. Despite no difference between groups in the shift in modified Rankin Scale scores at 90 days, an exploratory analysis raised the possibility of improved functional outcome with glibenclamide in patients with a baseline core infarct volume less than 125 mL.

Implications of all the available evidence

The findings of CHARM showed that intravenous glibenclamide did not improve functional outcome after large hemispheric infarction, although the trial was stopped early and, therefore, was underpowered to make definitive conclusions. However, specific cohorts of patients might benefit from the treatment, according to findings of prespecified and post-hoc subgroup analyses. These hypothesis-generating findings should be tested further in a prospective phase 3 trial.

hemispheric infarction and carries a high risk of death and disability.[2,3] Prevention of oedema might counteract the harmful effects of post-ischaemic injury. Decompressive craniectomy can reduce the risk of death and severe disability from cerebral oedema, but this invasive procedure can only be carried out in a subset of patients.[3] Osmotherapy is used as a reactive treatment for brain oedema but is not proven to improve clinical outcomes.[3] To date, no pharmacological therapy has been investigated for the prevention of oedema in patients. The only approved drug therapy for acute ischaemic stroke is thrombolysis with intravenous recombinant tissue plasminogen activator (rtPA). In recent years, endovascular reperfusion (thrombectomy) has been investigated for the treatment of acute ischaemic stroke with large vessel occlusion, including large hemispheric infarction.[4–8] However, as many as 70% of patients treated with endovascular thrombectomy remain disabled, highlighting a considerable unmet need for effective brain protection strategies to improve stroke outcomes.[9]

The pathophysiology of cerebral oedema could suggest potential targets for treatment. After ischaemia, the sulfonylurea receptor 1 (SUR1) co-associates with transient receptor potential melastatin 4 (TRPM4) to form a non-selective cation channel that is upregulated de novo by all major cell types of the neurovascular unit, and this channel has been implicated in oedema formation.[10,11] Sodium influx through the newly expressed SUR1–TRPM4 channel in astrocytic endfeet facilitates calcium–calmodulin-dependent translocation of aquaporin-4 to the plasma membrane and water influx.[11] Pharmacological blockade of this channel with the SUR1 inhibitor glibenclamide in animal models of stroke led to attenuated oedema formation and a reduction in necrotic cell death.[12] Rodent models of large vessel occlusion, with and without thrombolysis and in comparison with decompressive craniectomy, showed that glibenclamide treatment was associated with decreased haemorrhagic transformation, increased tissue perfusion, and improved survival and behavioural outcomes.[13,14] These data are consistent with Stroke Treatment Academic Industry Roundtable (STAIR) guidance, including independent replication and testing in humans.[15] Furthermore, a multi-step mechanism involving sequential gene activation, channel assembly, and transport to the cell membrane suggests that it takes time for SUR1–TRMP4 to affect water transport.[16] This finding, combined with the fact that the principal pathophysiological target—brain swelling—takes hours to develop, suggests that a treatment window of 10 h should be available for glibenclamide administration following the onset of ischaemia.[17]

To investigate whether prevention or reduction of oedema might improve neurological outcomes, it is important to characterise the cohort of patients who reliably experience neurological deterioration due to brain swelling after stroke. In prospective observational studies, an early infarct volume of 82 mL or greater was strongly associated with clinically significant oedema and was included among enrichment criteria for proof-of-concept trials of glibenclamide.[18] Two phase 2 studies showed the safety, feasibility, and preliminary efficacy of intravenous glibenclamide—GAMES-Pilot[19] and GAMES-RP.[20] The GAMES-Pilot study enrolled ten patients with severe stroke (mean diffusion weighted imaging 101 mL) in an

open-label design and demonstrated the feasibility of enrolment of a critically ill stroke population, with a mortality rate of 10%.[19] The GAMES-RP trial was a randomised, double-blind, placebo-controlled trial conducted at 18 centres; 86 patients with large hemispheric infarction (core volume 82–300 mL) were enrolled and treated with intravenous glibenclamide or placebo infusion within 10 h of stroke onset.[20] Although GAMES-RP was neutral for the primary composite endpoint (90-day modified Rankin Scale [mRS] score of 0–4 without decompressive craniectomy), patients younger than 70 years treated with intravenous glibenclamide had significantly improved functional outcomes and significantly less frequent neurological or oedema-related death compared with those administered placebo.[21,22]

The CHARM trial was designed to replicate the preliminary results seen in GAMES-RP. In this phase 3 trial, we aimed to investigate whether functional outcome at 90 days (as assessed by the shift in mRS scores) would be better in patients with large hemispheric infarction treated with intravenous glibenclamide versus those receiving placebo.

Methods

Study design

CHARM was a phase 3, double-blind, placebo-controlled randomised trial conducted at 143 acute stroke centres in 21 countries. The trial was conducted in accordance with the Declaration of Helsinki and the International Council for Harmonisation of Good Clinical Practice guidelines. Ethics approval was obtained by the relevant regulatory bodies in each country at the local, regional, or national level, as appropriate. The trial protocol was approved by an institutional review board at each participating site. The protocol and statistical analysis plan are included in the appendix.

Study monitors verified source data and reviewed local adverse event reporting. An academic steering committee oversaw the trial. A data and safety monitoring board (DSMB)—comprising experts in vascular and critical care neurology and a statistician—oversaw patient safety and was responsible for conducting an unblinded interim analysis to assess futility.

CHARM is registered with ClinicalTrials.gov (NCT02864953). The trial sponsor decided to terminate CHARM early for strategic and operational reasons (ie, slower than planned enrolment due to COVID-19), without any safety concerns or knowledge of efficacy outcomes. Enrolment was stopped in May, 2023, and procedures were initiated by the sponsor to close the study, complete follow-up of enrolled patients, and perform database lock and the statistical analysis.

Participants

All enrolled patients or their legally authorised representatives provided written informed consent. Electronic remote consent from legally authorised representatives was used where available. Eligible patients were aged 18–85 years with a clinical diagnosis of acute ischaemic stroke in at least the middle cerebral artery territory within 10 h of stroke onset, a US National Institutes of Health Stroke Scale (NIHSS) score of 10 or higher, absence of significant premorbid disability as assessed by the site investigator, and a core lesion of 80–300 mL, as assessed by CT perfusion (RAPID, IschemaView; Golden, CO, USA) or diffusion-weighted imaging. If CT perfusion or MRI was not available to determine core lesion volume, we used non-contrast CT to determine eligibility with the Alberta Stroke Program Early CT Score (ASPECTS); we included patients with an ASPECTS of 1–5 involving at least two cortical regions. In patients with wake-up stroke, stroke onset time was defined as the midpoint between sleep onset and waking. The timing of dosing up to 10 h after stroke onset was selected on the basis of data from animal studies and early-phase trials.

Since experience with thrombectomy for the treatment of large hemispheric infarction was minimal at the time of trial initiation,[9] the maximum number of participants treated with thrombectomy before study entry was originally set at 8%. During the conduct of the study, and given the changing standards of practice,[9] this percentage was increased to 20% by June, 2021. For patients who underwent thrombectomy, a post-thrombectomy MRI was required for ascertainment of the qualifying infarct volume.

Randomisation and masking

Patients were screened for eligibility by clinical teams at each site and enrolled by study site personnel. Eligible patients were randomly assigned to either intravenous glibenclamide or placebo (1:1) using a centralised web-based randomisation algorithm. Randomisation was done with interactive response technology by a contract research organisation that had no further role in the trial. A minimisation method was used to ensure treatment groups were balanced for the following baseline covariates: geographical region; rtPA treatment; endovascular thrombectomy; mode of entry (ASPECTS *vs* CT perfusion or diffusion MRI); and baseline NIHSS (10–20 *vs* >20). The funder, principal investigators, site investigators, patients, imaging core, and outcomes personnel were masked to treatment allocation. Drug vials, preparation bags, and tubing were identical for both treatment groups.

Procedures

Intravenous glibenclamide (or matching placebo) was administered as a bolus followed by 72-h infusion, for a total dose of 8·6 mg. Standard-of-care reperfusion interventions—such as rtPA and endovascular thrombectomy—were permitted, in accordance with local stroke guidelines. Additional interventions used in patients with large stroke and swelling (eg, mannitol,

hypertonic saline, and decompressive craniectomy) were also allowed. Other aspects of medical management and intensive care, including blood pressure and temperature management, were implemented in line with local policies and based on guidelines from professional organisations such as the American Heart Association, the Neurocritical Care Society, and the German Society for Neurocritical and Emergency Medicine.[3,23] A central imaging core (Bioclinica, Clario, Philadelphia, PA, USA) was used for quality control of site-determined imaging eligibility and measurement of imaging endpoints. Data collection was maintained in an electronic data capture system through a contract research organisation.

Outcomes

The primary outcome was a shift in the distribution of scores on the mRS at 90 days. With this ordinal scale, a score of 0 indicates no disability and 1 indicates no significant disability, despite mild symptoms. A score of 5 indicates severe disability and a bedridden state, and 6 is death. As the health state transition between 0 and 1 was expected to be uninformative due to its rarity in this severely affected population, levels 0 and 1 were combined into a single level. As a substantial proportion of patients consider the health state transition between 5 and 6 to have no clinical value, levels 5–6 were also combined, resulting in a five-level ordinal scale. The mRS score was assessed by a certified rater who was not aware of treatment assignment, with version 3.0 of the Rankin Focused Assessment.[24] If an in-person assessment was not possible then a telephone assessment was performed.

The secondary outcomes were, in rank order: mortality up to 90 days; proportion of participants who did not require constant care (defined as an mRS score of 0–4); and midline shift on neuroimaging at 72 h. Midline shift was defined as the perpendicular distance between the septum pellucidum and the line drawn between anterior and posterior attachments of the falx to the inner table of the skull, and was assessed by two central readers masked to treatment assignment. The average of both readers was used for analysis.

The key safety outcomes were the incidence of serious adverse events and clinically significant abnormal vital signs and laboratory results (including those associated with blood glucose concentrations). Given the known effect of glibenclamide in reducing serum blood glucose, hypoglycaemia was prespecified as an adverse event of special interest and was upgraded to a serious adverse event if the glucose concentration was confirmed to be lower than 55 mg/dL. The study incorporated a protocol to manage hypoglycaemia in anticipation of this effect.

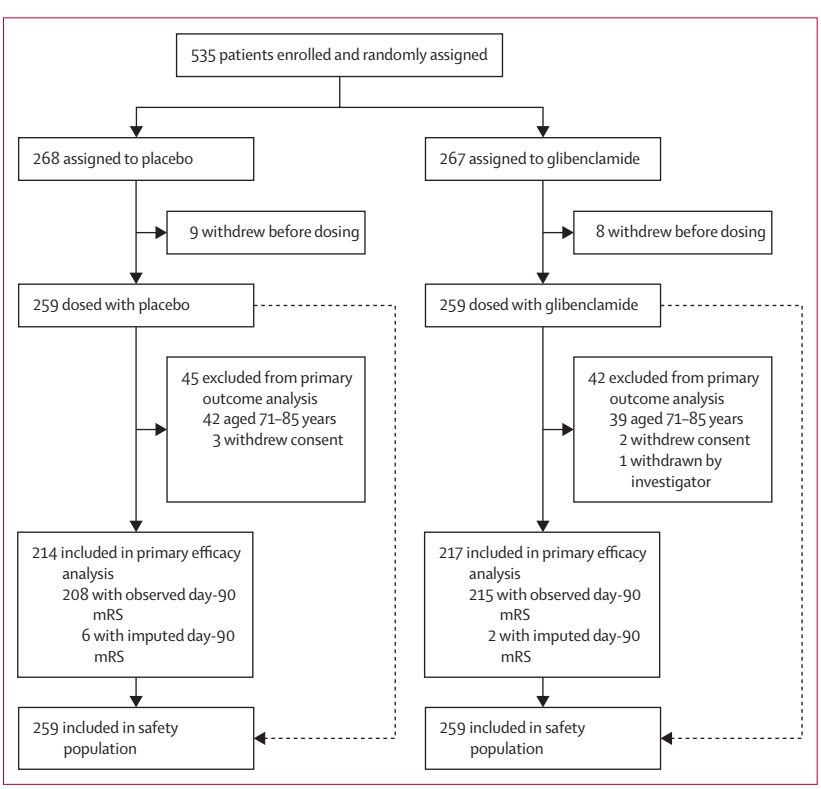

Figure 1: **Trial profile**
mRS=modified Rankin Scale.

Statistical analysis

The primary efficacy analysis population was prespecified to comprise patients aged 18–70 years who received any study drug and had at least one post-baseline mRS score before day 90. Previous studies have suggested that patients older than 70 years with severe stroke are at high risk of death due to withdrawal of care.[25] For this reason, patients aged 71–85 years were enrolled but only included in the safety analysis. The number of participants aged 71–85 years was capped at 80.

Based on observed 90-day mRS distributions in the phase 2 GAMES-RP trial,[20] we estimated that a sample size of 327 patients (aged 18–70 years) per intervention group would have approximately 90% power to detect an odds ratio of 1·595 in shifting the distributions of the five-category mRS in the direction of lower disability. The power calculation used logistic regression to detect an effect size at a two-sided 5% significance level. Assuming up to 5% of the sample would not be evaluable for the primary analysis, the trial was designed to enrol a maximum of 688 participants aged 18–70 years.

Full details about the outcome analyses are provided in the statistical analysis plan in the appendix. In brief, the primary endpoint was analysed with ordinal logistic regression (proportional odds model), and the model was adjusted for baseline randomisation strata that included region, rtPA (yes or no), thrombectomy (yes or no), use of ASPECTS for screening (yes or no), and baseline NIHSS (≤20 *vs* >20). The proportional odds assumption was tested and met; therefore, the results are presented as a common odds ratio (cOR). The secondary outcome analyses for time to all-cause death up to day 90, the

proportion of participants with mRS 0–4 at day 90, and midline shift at 72 h were also adjusted for baseline strata. To control for type 1 error, a sequential closed testing procedure was used for secondary endpoints such that if statistical significance was not achieved for an endpoint, all endpoints of a lower rank for that comparison were considered not statistically significant.

For the primary outcome based on the 90-day mRS score, missing data were imputed with the use of a multiple imputation strategy. Two participants in the glibenclamide group and six participants in the placebo group had missing 3-month mRS scores. Due to the unexpected amount of missing data in the midline shift values, additional comparisons were performed to evaluate whether the missingness was non-random and to identify baseline covariates associated with missingness.

Heterogeneity of treatment effect was explored for the primary endpoint in six predefined subgroups of baseline characteristics: patients receiving intravenous rtPA at baseline; those treated with endovascular thrombectomy at baseline; geographical regions; baseline NIHSS dichotomised at 20 or lower; use of ASPECTS for enrolment; and wake-up stroke. Given the potential for a treatment effect in some of these subgroups, an additional hypothesis-generating analysis was conducted to evaluate treatment effect based on baseline stroke volume to inform future trial design (appendix).

A prespecified interim analysis was done to assess futility when 30% of participants in the planned primary analysis population completed the day 90 visit. The interim analysis included an option for a sample size re-estimation, but this was not ultimately considered. The DSMB reviewed the unblinded results and issued a recommendation to the sponsor to continue the trial based on the prespecified futility criteria not being met. The sponsor remained masked to the futility analyses.

Role of the funding source

The sponsor assembled an advisory committee consisting of academic leaders in stroke for further input and finalised the study design. The sponsor also assembled an independent DSMB consisting of senior academic leaders. The trial was funded by Biogen, and the sponsor provided the study drug and placebo to all sites. The sponsor funded the contract research organisation, which collected data. The analysis was performed by a statistician funded by the sponsor; however, the statistician analysed data in accordance with the statistical analysis plan. The funder had no role in the writing of the report or the decision to submit the manuscript for publication.

Results

Between Aug 29, 2018, and May 23, 2023, 535 participants were enrolled, of whom 17 did not receive a dose and were excluded from efficacy and safety analyses (figure 1). 81 were aged 71–85 years and were only included in the safety analyses. Of the remaining participants, 431 met criteria for the primary analysis population that contributed to the efficacy analysis: 217 participants were assigned to intravenous glibenclamide and 214 received a placebo infusion. Eight (2%) patients were lost to follow-up at day 90.

Baseline demographic, clinical, and imaging characteristics were similar between the two groups (table 1). The median NIHSS score was 19 (16–23) in the placebo group

	Placebo (n=214)	Glibenclamide (n=217)
Age, years	58·7 (9·0)	58·0 (9·5)
Sex		
Female	73/214 (34%)	70/217 (32%)
Male	141/214 (66%)	147/217 (68%)
Race		
White	131/214 (61%)	141/217 (65%)
Black	19/214 (9%)	17/217 (8%)
Asian	44/214 (21%)	44/217 (20%)
Other	12/214 (6%)	14/217 (6%)
Ethnicity		
Hispanic	29/214 (14%)	34/217 (16%)
Non-Hispanic	185 (86%)	183 (84%)
Pre-stroke mRS		
0	182/214 (42%)	178/217 (41%)
1	15/214 (4%)	19/217 (4%)
2	6/214 (1%)	3/217 (1%)
NIHSS score	19 (16–23)	19 (16–22)
rtPA administration	84/214 (39%)	82/217 (38%)
Endovascular thrombectomy	40/214 (19%)	42/217 (19%)
Reperfusion (mTICI score ≥2b)	34/82 (85%)	31/82 (74%)
Enrolment imaging modality		
Brain MRI	82/214 (38%)	65/217 (30%)
DWI ischaemic core volume, mL	141 (105–191)	125 (100–175)
CT perfusion	66/214 (31%)	76/217 (35%)
Ischaemic core volume, mL	131 (93–167)	133 (104–176)
Non-contrast CT	66/214 (31%)	76/217 (35%)
ASPECTS	4 (2–4)	3 (2–4)
Region randomisation stratification		
North America	86/214 (40%)	86/217 (40%)
Europe	59/214 (28%)	66/217 (30%)
Pacific region	69/214 (32%)	65/217 (30%)
Stroke onset to rtPA, h	2·5 (1·0)	2·4 (1·1)
Stroke onset to arterial puncture, h	4·0 (1·9)	4·7 (2·2)
Stroke onset to imaging, h	5·4 (2·6)	5·7 (2·8)
Stroke onset to randomisation, h	7·8 (2·2)	8·1 (2·3)
Stroke onset to study drug start, h	8·9 (2·1)	9·2 (2·1)

Data are n/N (%), mean (SD), or median (IQR). mRS=modified Rankin Scale. NIHSS=US National Institutes of Health Stroke Scale. rtPA=recombinant tissue plasminogen activator. mTICI=modified treatment in cerebral infarction. DWI=diffusion-weighted imaging. ASPECTS=Alberta Stroke Program Early CT Score.

Table 1: **Baseline demographics of the primary efficacy population (modified intention-to-treat population)**

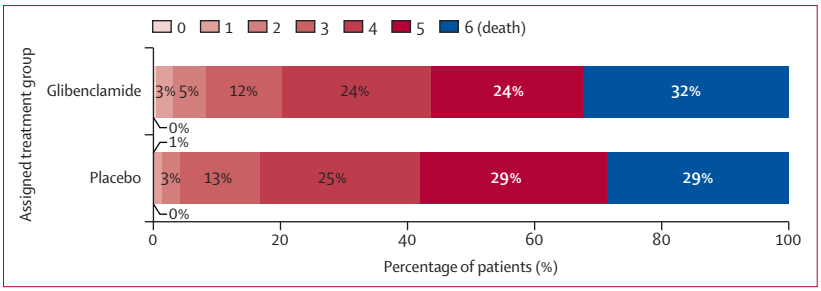

Figure 2: **Distribution of mRS score at 90 days**
The percentage of participants achieving each score on the mRS (0–6) is shown for both treatment groups. mRS=modified Rankin Scale.

	Placebo (n=214)	Glibenclamide (n=217)	Treatment effect (95% CI)*	p value
Primary outcome†				
Median modified Rankin Scale score at 90 days	5 (4 to 6)	5 (4 to 6)	1·17 (0·80 to 1·71)	0·42
0–1	3/214 (1%)	7/217 (3%)	..	..
2	6/214 (3%)	11/217 (5%)	..	..
3	27/214 (13%)	26/217 (12%)	..	..
4	54/214 (25%)	51/217 (24%)	..	..
5–6	124/214 (58%)	122/217 (56%)	..	..
Secondary outcomes				
Mortality	61/214 (29%)	70/217 (32%)	1·20 (0·85 to 1·70)	0·30
Modified Rankin Scale of 0–4 at 90 days	89/214 (42%)	93/217 (43%)	1·07 (0·72 to 1·60)	0·74
Mean midline shift at 72 h, mm	6·3 (4·8)	7·0 (4·6)	0·82 (–0·23 to 1·87)	0·11
Midline shift measurement available‡	150/214 (70%)	155/217 (71%)	..	..

Data are n/N (%), median (IQR), or mean (SD), unless otherwise stated. *The treatment effect is common odds ratio for the primary outcome and dichotomised modified Rankin Scale secondary outcome, hazard ratio for mortality, and mean difference for midline shift. †A five-category modified Rankin Scale was used for the logistic regression model and combines categories 0 and 1, and categories 5 and 6. ‡Measured scans included any scan (head CT or MRI) between 24 h and 102 h, or before decompressive craniectomy or withdrawal of care, if earlier. Because the primary outcome was not significant, secondary outcomes p values should be considered nominal.

Table 2: **Primary and secondary outcomes in the primary efficacy population (modified intention to treat)**

	Placebo (n=259)	Glibenclamide (n=259)
Number of patients with any serious adverse event	177 (68%)	199 (77%)
Number of patients with any adverse events leading to drug withdrawal	24 (9%)	24 (9%)
Number of patients with serious adverse event of hypoglycaemia	4 (2%)	15 (6%)
Parenchymal haematoma type 1 or 2	19 (7%)	22 (8%)
Decompressive craniectomy	68 (26%)	69 (27%)

Data are n (%).

Table 3: **Safety outcomes in all study participants who received a dose**

and 19 (16–22) in the glibenclamide group, and the mean time between when patients were last known well and study drug bolus was 8·9 h (SD 2·1) in the placebo group and 9·2 h (2·1) in the glibenclamide group. The median baseline infarct volume on CT perfusion was 131 mL (IQR 93–167) in the placebo group and 133 mL (104–176) in the glibenclamide group; in those assessed by diffusion weighted imaging MRI, it was 141 mL (105–191) in the placebo group and 125 mL (100–175) in the glibenclamide group. Among those enrolled with non-contrast CT, the median ASPECTS was 4 (IQR 2–4) in the placebo group and 3 (2–4) in the glibenclamide group. Intravenous thrombolysis was administered in 166 (39%) patients (84 in the placebo group and 82 in the glibenclamide group), and 82 (19%) underwent endovascular thrombectomy of a large vessel occlusion (40 in the placebo group and 42 in the glibenclamide group). Following thrombectomy, 34 (85%) achieved mTICI 2b or greater reperfusion in the placebo group, as did 31 (74%) in the glibenclamide group.

Treatment with glibenclamide was not associated with a difference in disability on the mRS at 90 days compared with placebo (cOR 1·17 [95% CI 0·80–1·71]; p=0·42; figure 2, table 2). The time to all-cause mortality did not differ between the two treatment groups (hazard ratio 1·20 [95% CI 0·85–1·70]; p=0·30). The proportion of patients who did not require constant care, defined as a score on the mRS of 0–4 at 90 days, was 43% (93 of 217) in the glibenclamide group and 42% (89 of 214) in the placebo group (odds ratio 1·07 [95% CI 0·72–1·60]; p=0·74). The mean midline shift at 72 h was 7·0 mm (SD 4·6) in the glibenclamide group and 6·3 mm (4·8) in the placebo group (mean difference 0·82 [–0·23 to 1·87]; p=0·11). However, midline shift values were missing in 126 (29%) patients (64 in the placebo group and 62 in the glibenclamide group), and those with missing values had baseline differences including a younger age, worse neurological deficits (reflected in a higher NIHSS score), and a larger baseline stroke volume or a worse ASPECTS (appendix).

Serious adverse events occurred in 199 (77%) patients in the glibenclamide group and 177 (68%) patients in the placebo group (table 3). Serious adverse events of one or more episodes of hypoglycaemia occurred in 15 (6%) patients with glibenclamide and four (2%) with placebo, leading to dose interruption or reduction in seven (3%) patients with glibenclamide and in one (<1%) with placebo. The number of drug withdrawals did not differ between treatment groups. Rates of intracerebral haematoma (parenchymal haematoma type 1 or type 2) and of decompressive craniectomy were also similar between treatment groups (table 3).

The shift in the degree of disability within prespecified subgroups in the primary analysis population is shown in figure 3. Subgroup analyses revealed a hypothesis-generating signal of efficacy in patients treated with reperfusion treatment (rtPA and endovascular thrombectomy), less severe stroke (NIHSS ≤20), and wake-up stroke, consistent with experimental and early-phase trial data. To further explore the effect of stroke severity, the primary endpoint was evaluated sequentially in a post-hoc analysis based on the initial stroke volume among those patients enrolled with MRI or CT perfusion, which identified a

potential threshold of 125 mL, below which there seemed to be a favourable effect of glibenclamide (appendix).

Discussion

In the phase 3 CHARM trial, intravenous administration of glibenclamide did not reduce disability at 90 days in patients with a large hemispheric stroke, according to a shift analysis of mRS scores. However, when examined across various subgroups, including post-hoc analyses by baseline infarct volumes and in patients who underwent endovascular treatment, favourable results supported previous findings from the phase 2 GAMES-RP study, which showed preliminary evidence of a reduction in mortality and improvement in functional outcome.[20–22] The safety analysis of the CHARM trial confirmed the overall high rate of serious adverse events in this critically ill population, consistent with earlier phase studies.[19,20] There was also an expected higher frequency of hypoglycaemia among patients treated with glibenclamide, and dose-reduction strategies specified by the trial protocol were able to manage low blood glucose concentrations.

The CHARM trial was designed to extend the preliminary findings of the GAMES-RP trial to a larger and more generalised population presenting with oedema due to large hemispheric infarction. The reasons for the neutral results in CHARM might be due to alterations in trial design, changes in standard of care, or differences in the study participants. First, the phase 2 GAMES-RP trial relied on brain MRI to ascertain eligibility. In CHARM, however, three different neuroimaging modalities were used to ascertain eligibility, to account for differences in standard-of-care imaging evaluation of patients with acute stroke across centres. Although a minimisation strategy was used during randomisation, numerically more patients were enrolled via CT ASPECTS criteria, and more patients with severe stroke were assigned to the glibenclamide group. Second, GAMES-RP was conducted at 18 centres in the USA, whereas CHARM was conducted at more than 100 centres across 21 countries, raising the possibility that practice variation in intensive and neurological care might affect evaluation of efficacy. Finally, thrombolysis was used in 61% of GAMES-RP participants versus 39% in CHARM, which is reflective of likely variation in the use of thrombolysis across countries in CHARM.

A prespecified analysis in CHARM identified subgroups that warrant further investigation in order to ascertain potential benefit from intravenous glibenclamide treatment. In accordance with other recent acute stroke trials,[26] patients with wake-up stroke were enrolled, with stroke onset time defined as the midpoint of sleep onset and awakening. Because stroke onset in patients with wake-up stroke might be close to awakening, these participants in the CHARM trial might have received the study drug earlier in the 10 h time window. Whether there is a time–treatment effect interaction is unknown and requires investigation in future trials. In a post-hoc analysis, examination of treatment effect by baseline infarct volume, particularly in patients who had reperfusion treatment, suggested that glibenclamide might improve outcomes up to a lesion volume of 125 mL, a ceiling generally consistent with findings from recent large core endovascular thrombectomy trials.[27,28] This finding also merits further study.

In the previous GAMES-RP study,[20] patients treated with endovascular thrombectomy were not included. In the time between GAMES-RP and CHARM, the standard of care for acute stroke has changed to incorporate the use of endovascular reperfusion for acute ischaemic stroke,[29] including recent evidence of its benefits in large hemispheric infarction.[4–8] However, considerable morbidity was noted across individual large core thrombectomy trials, which showed an inconsistent or null effect above the 125 mL threshold.[27,28] In accordance with this evolution in clinical practice, approximately 20% of the cohort in CHARM underwent endovascular treatment. In the subgroup analysis of patients who had endovascular thrombectomy, a hypothesis-generating signal of efficacy was noted, and in a post-hoc analysis, this signal was also seen below a baseline stroke volume threshold of approximately 125 mL. These data support the hypothesis that there might be a ceiling effect for infarct volumes above this size in large hemispheric infarction. Moreover, the inclusion of participants above such a ceiling might obscure the ability to detect an

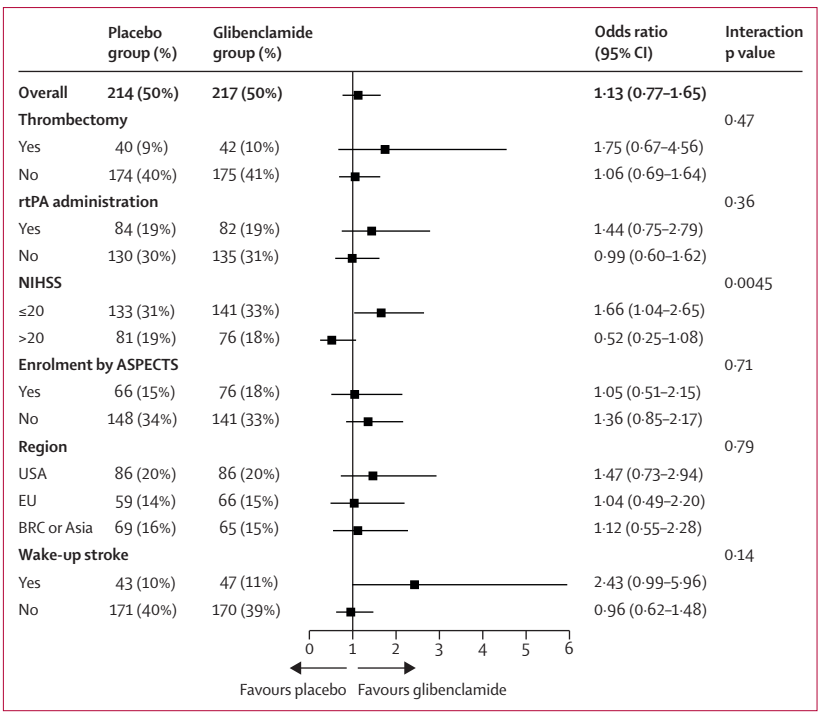

Figure 3: **Analyses of the primary outcome among prespecified subgroups**
A forest plot for each subgroup is shown, where an odds ratio higher than 1·0 indicates less disability on the mRS at 90 days. ASPECTS=Alberta Stroke Program Early CT Score. BRC=Brazil, Russia, China. NIHSS=US National Institutes of Health Stroke Scale. mRS=modified Rankin Scale. rtPA=recombinant tissue plasminogen activator.

efficacy signal and could inform the design of future trials for brain protection.

The CHARM trial represents an innovative approach to stroke translation. Data from animal studies show that glibenclamide is protective for all cell types that comprise the neurovascular unit. Molecular data from animal studies support an anti-oedema-related mechanism of action and provide the basis for a prolonged treatment time window. The pharmacological target SUR1–TRPM4 is conserved across rodent models of stroke and ex-vivo human brain tissue. Although recent large core trials have shown a benefit of endovascular thrombectomy,[6–8] stroke survivors continue to have high rates of severe disability. Due to the considerable morbidity attributable to oedema, particularly in younger stroke patients, a significant unmet medical need remains. There are no successful therapies for preventing brain swelling. Data from this trial, in combination with results from recent large ischaemic core endovascular thrombectomy trials, suggest this cohort might be ideal for further study of glibenclamide.

Limitations of the CHARM trial include the high degree (almost 30%) of missing data for midline shift measurements. The missingness was non-random and more frequent among severely affected patients, making interpretation of this neuroimaging outcome measure more difficult and uncertain. From the available data, the reduction of midline shift that was seen in the phase 2 GAMES-RP trial was not observed in CHARM. Another key limitation was lower than expected enrolment rates following the COVID-19 pandemic, and a strategic business decision by the sponsor to stop the trial early. However, the trial had completed an interim analysis, achieved approximately 70% of the target enrolment, and all outcomes were ascertained in enrolled patients before any knowledge of unblinded safety or efficacy data. These procedures were overseen by an independent DSMB. However, conclusions are not definitive and must still be interpreted cautiously because the trial was underpowered. A final limitation is that two-thirds of patients were male, and future trials should enrol more female patients in order to further increase the generalisability of the results.

A key strength of the CHARM trial is the enrolment of a broad population of patients with large hemispheric infarction without restrictions of standard of care. The trial design also involved continuous administration of study drug to avoid the peak and trough effects of intermittent oral administration, thus ensuring continuous SUR1 inhibition, which might not be achieved in oral dosing strategies.[30] In preclinical studies, a novel, large-stroke, high-mortality animal model characterised by oedema formation was developed to mirror the human condition.[14] In both GAMES-RP and CHARM, patients with very large core stroke were successfully identified and enrolled in the hyperacute phase. A main cause of morbidity and mortality in this population is cerebral oedema, for which there have been no pivotal trials of pharmacotherapy in decades. Several recent trials of endovascular reperfusion have shown the efficacy of reperfusion in this patient population.[6–8] However, reperfusion injury and oedema continue to be persistent causes of morbidity in this population, even in these successful trials.[7]

The results of the CHARM trial did not show an improvement in functional outcome at 90 days in participants with large hemispheric infarction treated with glibenclamide. Subgroup data from CHARM suggest that further prospective evaluation of intravenous glibenclamide could be warranted in the setting of reperfusion. The consistent safety profile and identification of a responsive population, consistent with experimental models and previous clinical data, warrant validation in a dedicated randomised controlled trial with a ceiling on extreme infarct volumes in patients who undergo reperfusion treatment.

Contributors

KNS and WTK, global leads for the trial, designed the trial largely based on the phase 2 study, GAMES-RP, which they also led. KNS, GWA, JLS, BCVC, BJM, HEH, CC, TS, KT, MWi, RGN, JMS, MWa, KD and WTK developed the study protocol. KNS and WTK interpreted the data and wrote the first draft of the manuscript with input from all authors. RL, JC, and NL analysed the data. KNS, MWi, MWa, KD, and WTK had complete access to and verified all the data in the study. KNS and WTK were responsible for the decision to submit the manuscript for publication. All authors edited the manuscript and take responsibility for the accuracy of the data and trial fidelity.

Declaration of interests

KNS has received research support from Biogen administered as a grant to Yale University; other research support from the US National Institutes of Health (NIH), American Heart Association, and Hyperfine, received consulting fees from CSL Behring, Rhaeos, Cerevasc, Astrocyte, Bexorg, and Brain Q; owns equity in Alva Health as a co-founder; and has served on data safety and monitoring board for Zoll, Sense, and Phillips. GWA has received consulting fees from Biogen related to the conduct of the CHARM trial; consulting fees from Genentech and RapidAI; and has equity in RapidAI. JLS has received consulting fees for advising on rigorous and safe clinical trial design and conduct from Biogen, Medtronic, Phenox, and Rapid Medical. BJM has received research support from Biogen administered as a grant to their previous institution (University of Pittsburgh Medical Center); has received grant funding from the NIH; and has equity interest in Celdara Medical. HEH has received consulting fees from Biogen related to the conduct of the CHARM trial; consulting fees from RapidAI; and grant funding from the NIH. CC has received research funding from Biogen related to the conduct of the CHARM trial in France; grant funding from French Ministry of Health and Agence Nationale de la Recherche; and consulting fees from Bayer. KT has received lecture fees from Daiichi-Sankyo, Otsuka, Janssen, Bayer, and Bristol Myers Squibb. RL is an employee of Biogen. MWa, RL, JC, NL, and KD are employees and stockholders of Biogen. RGN reports consulting fees for advisory roles with Anaconda, Biogen, Cerenovus, Genentech, Philips, Hybernia, Hyperfine, Imperative Care, Medtronic, Phenox, Philips, Prolong Pharmaceuticals, Stryker Neurovascular, Shanghai Wallaby, and Synchron; and stock options for advisory roles with Astrocyte, Brainomix, Cerebrotech, Ceretrieve, Corindus Vascular Robotics, CrestecBio, Euphrates Vascular, Vesalio, Viz-AI, RapidPulse, and Perfuze. RGN is one of the Principal Investigators of the "Endovascular Therapy for Low NIHSS Ischemic Strokes (ENDOLOW)" trial; is the Principal Investigator of the "Combined Thrombectomy for Distal MediUm Vessel Occlusion StroKe (DUSK)" trial; and is an investor in Viz-AI, Perfuze, Cerebrotech, Reist/Q'Apel Medical, Truvic, Tulavi Therapeutics, Vastrax, Piraeus Medical, Brain4Care, Quantanosis AI, and Viseon. JMS has received grant funding from the NIH and US Department of Veterans Affairs; consulting fees from Biogen; and owns stocks or options from Remedy Pharmaceuticals,

Martin Pharmaceuticals, and Woolsey Pharmaceuticals. WTK has received research funding from Biogen related to the conduct of the CHARM trial; grant funding from the NIH, the American Heart Association, and the Alzheimer's Association; research funding from NControl Therapeutics; research funding from Hyperfine; consulting fees from Biogen, Acasti Pharma, and Astrocyte Pharmaceuticals; and owns stocks or options from Woolsey Pharmaceuticals and Acasti Pharma. BC and MWi declare no competing interests.

Data sharing

Patient-level data, study-level data, case report forms, or protocols, or both, can be shared with qualified scientific researchers who provide a methodologically sound proposal. Data will be made available on request via email to KS or WTK (kevin.sheth@yale.edu or wtkimberly@mgh.harvard.edu) beginning 12 months following publication to investigators whose proposed use of the data has been approved by the publications committee. Following approval, de-identified data and documents will be shared under data use agreements that further protect against participant re-identification.

Acknowledgments

We thank the country lead investigators and all the site investigators for their efforts in conducting the trial. Members of the independent data and safety monitoring board included Karen Johnston and Stephan Mayer. We also recognise funding from the sponsor, Biogen. The country lead investigators included: Bruce Campbell (Australia), Gisele Silva (Brazil), Andrew Demchuk (Canada), Daniel Strbian (Finland), Igor Sibon (France), Martin Köhrmann (Germany), Daniel Bereczki (Hungary), Natan Bornstein (Israel), Danilo Toni (Italy), Kazunori Toyoda (Japan), Vítor Cruz, Sang-Beom Jeon (South Korea), Marcel Arnold (Switzerland), Keith Muir, and Nikola Sprigg (UK).

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