

Long-Term Outcomes in Patients Aged ≤ 70 Years With Intravenous Glyburide From the Phase II GAMES-RP Study of Large Hemispheric Infarction An Exploratory Analysis

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Background and Purpose—We aimed to determine whether subjects aged ≤ 70 years who were treated with intravenous glyburide (RP-1127; BIIB093; glibenclamide) would have better long-term outcomes than those who received placebo.

Methods—GAMES-RP (Glyburide Advantage in Malignant Edema and Stroke—Remedy Pharmaceuticals) was a prospective, double-blind, randomized, placebo-controlled phase 2 clinical trial. Eighty-six participants, aged 18 to 80 years, who presented to 18 centers with large hemispheric infarction (baseline diffusion-weighted imaging volumes, 82–300 cm³) randomized within 10 hours of symptom onset were enrolled. In the current exploratory analysis, we included participants aged ≤ 70 years treated with intravenous glyburide (n=35) or placebo (n=30) who met per-protocol criteria. Intravenous glyburide or placebo was administered in a 1:1 ratio. We analyzed 90-day and 12-month mortality, functional outcome (modified Rankin Scale, Barthel Index), and quality of life (EuroQol group 5-dimension). Additional outcomes assessed included blood–brain barrier injury (MMP-9 [matrix metalloproteinase 9]) and cerebral edema (brain midline shift).

Results—Participants ≤ 70 years of age treated with intravenous glyburide had lower mortality at all time points (log-rank for survival hazards ratio, 0.34; $P=0.04$). After adjustment for age, the difference in functional outcome (modified Rankin Scale) demonstrated a trend toward benefit for intravenous glyburide-treated subjects at 90 days (odds ratio, 2.31; $P=0.07$). Repeated measures analysis at 90 days, 6 months, and 12 months using generalized estimating equations showed a significant treatment effect of intravenous glyburide on the Barthel Index ($P=0.03$) and EuroQol group 5-dimension ($P=0.05$). Participants treated with intravenous glyburide had lower plasma levels of MMP-9 (189 versus 376 ng/mL; $P<0.001$) and decreased midline shift (4.7 versus 9 mm; $P<0.001$) compared with participants who received placebo.

Conclusions—In this exploratory analysis, participants ≤ 70 years of age with large hemispheric infarction have improved survival after acute therapy with intravenous glyburide.

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Key Words: brain edema ■ glyburide ■ infarction ■ ischemic stroke ■ malignant infarction

Large hemispheric infarction (LHI) is a distinct form of arterial ischemic stroke characterized by marked tissue swelling that is often associated with herniation, death, or poor neurological outcome.^{1,2} Cerebral edema that occurs within the rigid cranial vault increases intracranial pressure, causing additional brain damage, and in many instances, herniation and

death. Current medical therapies for acute stroke and edema include head-of-bed elevation, osmotic therapy, sedation, and supportive care, but clinical trial evidence for these strategies is limited.²⁻⁴ In LHI, outcomes in patients ≤ 60 years of age may be improved with decompressive craniectomy^{1,2}—an invasive procedure with nontrivial complications.⁵

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Emerging studies have implicated the sulfonylurea receptor 1–transient receptor potential melastatin 4 channel as a mediator of edema formation and as a potential therapeutic target.⁶ Channel blockade in multiple preclinical models of stroke has demonstrated edema reduction and improved survival and neurological outcome.⁷ Ongoing efforts are evaluating whether this pathway may be a suitable therapeutic target in human stroke.⁸

Brain atrophy increases with age, particularly in individuals >70 years of age.⁹ Age-related cerebral atrophy in older patients may protect against space-occupying brain edema by providing room to compensate for the increase in volume.¹⁰ Several prior studies of LHI in adults have identified decreased age as a predictor of poor outcome.^{11–13} In addition, observational evidence suggests that patients >70 years of age have an increased frequency of withdrawal of care, especially in brain injuries where the initial insult is a major predictor of outcome.^{14,15} Therefore, subjects ≤70 years of age may be the most appropriate target population to test an intervention that reduces cerebral edema.

GAMES-RP (Glyburide Advantage in Malignant Edema and Stroke—Remedy Pharmaceuticals) was a randomized trial of intravenous glyburide versus placebo in patients aged 18 to 80 years at high risk for malignant cerebral edema, which found no difference in the primary outcome (composite outcome of decompressive craniectomy and functional outcome). However, there was decreased midline shift (MLS) in intravenous glyburide-treated subjects, and the results suggested a potential survival benefit for patients treated with glyburide.⁸ Here, we report an exploratory analysis of GAMES-RP in subjects ≤70 years of age, in which we evaluated whether treatment with intravenous glyburide would reduce MLS and decrease mortality. In addition to assessing 90-day outcomes in these subjects, we also evaluated their mortality, functional outcomes, disability, and quality of life at 1 year.

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Design and Subjects

GAMES-RP was a double-blind, randomized, placebo-controlled phase 2 trial of intravenous glyburide in subjects with anterior circulation LHI (baseline diffusion-weighted imaging volume of 82–300 cm³). The study enrolled patients aged 18 to 80 years from 18 centers in the United States who received study drug or placebo within 10 hours of symptom onset.⁸ The study methods and patient eligibility criteria have been reported.¹⁶ The study was approved by the institutional review boards at all participating centers. All participants or their legally authorized representatives provided written informed consent at enrollment. In this subgroup analysis, we included only subjects who were ≤70 years of age and who met per-protocol criteria. Key per-protocol criteria included administration of study drug or placebo and core laboratory verification of baseline infarction volume within the prespecified range (82–300 cm³).

Outcome Measurements

In the current subgroup analysis, we evaluated (1) functional outcome, measured with the modified Rankin Scale (mRS) including mortality^{11–13,17,18}; (2) activities of daily living, measured by the Barthel Index^{19,20}; and (3) health-related quality of life, evaluated with the EuroQol group 5-dimension (EQ-5D).^{21,22} Outcomes were

assessed at 90 days, 6 months, and 12 months. The EQ-5D utility score measures 5 domains of general health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and integrates the ratings into a single score, calculated using population-based preference weights for each subscale. In the present analysis, we used the weights obtained from the US population.^{23,24} Utility scores express health-related quality of life quantitatively as a fraction of perfect health, with a score of 1 representing perfect health and a score of 0 representing death. Outcomes were assessed either in person or by telephone by qualified raters blinded to treatment allocation. Additional outcomes included MLS and plasma concentration of MMP-9 (matrix metalloproteinase 9). MLS was measured by the blinded central imaging core on the day-4 magnetic resonance imaging. The midline was defined as the anatomic line anchored by the falx cerebri to the skull. MLS was drawn perpendicular at the point of maximum distention, at the level of the septum pellucidum.⁸ Total MMP-9 plasma concentration during study drug infusion at 24 to 72 hours (mean level of 3 daily samples) was measured with a commercially available assay (Human MMP-9 Quantikine ELISA; R&D Systems, Minneapolis, MN).

Statistical Analyses

All analyses were performed on the per-protocol sample, which included participants who had a centrally read DWI baseline lesion volume between 82 and 300 cm³ and who received any amount of the study drug or placebo. R (version 3.1.2) was used for all statistical analyses. Categorical variables were compared using Fisher exact test. Normally distributed continuous variables were summarized using means and SDs and were compared with *t* tests and 95% confidence intervals (CIs) for the mean. Non-normally distributed variables were summarized with medians and interquartile ranges, and distributions were compared using Mann–Whitney *U* tests. Shift analysis of the raw mRS scores at 90 days and 12 months was compared using the Mann–Whitney *U* test; effect sizes of the shift (common odds ratio [COR] and its 95% CI) were estimated using ordinal logistic regression. Multivariable analysis using generalized estimating equations with unstructured correlation matrix and robust jackknife variance estimate was used to evaluate the effect of intravenous glyburide on longitudinal clinical outcomes (Barthel Index, EQ-5D) at 90 days, 6 months, and 12 months.²⁵ Missing values because of death on the Barthel Index were imputed using the worst score for each group. For subjects lost to follow-up or missing a 12-month mRS, the last observed mRS value (90 days or 6 months) was carried forward. Kaplan–Meier methods were used to estimate survival. A Cox proportional hazards model compared survival between those who received study drug versus placebo. The ordinal logistic regression, generalized estimating equations, and Cox regression were adjusted for age (≤60 versus 61–70 years) to account for any potential imbalance in this major prognostic variable. All *P* values are reported as 2 sided. Because of the exploratory nature of this analysis, statistical significance was set at 0.05, unadjusted for multiple comparisons. A statistical trend was noted if the *P* value was between 0.05 and 0.10.

Results

Subject Characteristics

Of the 86 subjects randomized in GAMES-RP, 77 were included in the per-protocol analysis.⁸ Of these, 65 subjects were ≤70 years of age; 35 of these subjects were randomly allocated to intravenous glyburide and 30 to placebo. For this subgroup, the mean age was lower in the intravenous glyburide group when compared with placebo (55±9 versus 60±7 years; *P*=0.02, *t* test). We performed an age-by-treatment interaction analysis for functional outcome (*P*=0.19), and indeed, in the age 71 to 80 group, the COR point estimate was 0.67 (favoring placebo) but was 2.49 in the <70 group. None of the other baseline characteristics differed significantly between the 2 treatment groups

(Table 1). Two subjects were lost to follow-up after 90 days. There was no significant difference in the use of decompressive craniectomy between the 2 groups (37% in intravenous glyburide group versus 27% in placebo group; $P=0.43$).

Mortality, MLS, and MMP-9 Levels

All-cause mortality at 1 year was 5/35 (14%) in the intravenous glyburide group and 12/30 (40%) in the placebo group. The Kaplan–Meier curve presented in Figure 1 demonstrates that more deaths occurred in the placebo group within 30 days and that this group difference was sustained throughout the 12-month follow-up period. After adjusting for age, the

hazard ratio was 0.34 (95% CI, 0.12–0.96; $P=0.04$; Figure 1). The median MLS at the level of the septum pellucidum at 72 to 96 hours was 4.7 mm in the intravenous glyburide group versus 9.0 mm in the placebo group ($P=0.001$, t test). Patients treated with intravenous glyburide had significantly lower concentrations of total MMP-9 compared with those treated with placebo (mean, 189 versus 367 ng/mL; $P=0.001$, t test).

Functional Outcomes

In an unadjusted analysis, functional outcome at 90 days was better among subjects who received intravenous glyburide compared with those who received placebo (COR, 2.49; 95% CI, 1.02–6; $P=0.05$; Figure 2). There was a slight reduction in the effect size during 12 months (COR, 2.24; 95% CI, 0.92–5.46; $P=0.08$). Although not statistically significant after adjusting for age group, the shift in the mRS still favored intravenous glyburide at 90 days (adjusted COR, 2.31; 95% CI, 0.93–5.72; $P=0.07$) and 12 months (adjusted COR, 2.11; 95% CI, 0.86–5.18; $P=0.10$).

An additional analysis among participants who did not undergo decompressive craniectomy showed a point estimate of the COR was 2.84 (P value of 0.063).

Subjects treated with intravenous glyburide had higher scores on the Barthel Index and EQ-5D at all time points when compared with patients who received placebo (Table 2). Repeated measures analysis at 90 days, 6 months, and 12 months showed a significant treatment effect of intravenous glyburide on Barthel Index (95% CI, 2.1–37; $P=0.03$) and EQ-5D (95% CI, 0.001–0.249; $P=0.05$) after adjusting for age. Because of the possibility that long-term outcomes were driven by an early difference in mortality between groups, we performed an additional analysis on survivors, which did not show a difference between groups (Table 3). Figure 3 illustrates the time trend in treatment effect for both outcome variables (Barthel Index and EQ-5D).

Discussion

We present the results of an exploratory analysis of 12-month outcomes in subjects from the GAMES-RP study who were aged ≤ 70 years. Though the age–treatment interaction did not reach significance ($P=0.19$), participants in the subgroup who received intravenous glyburide had improved survival compared with those who received placebo. Although the primary efficacy analysis from GAMES-RP⁸ did not meet the prespecified efficacy end point, these data suggest that patients ≤ 70 years of age, who may be at higher risk of adverse clinical outcomes from cerebral edema, may benefit from therapy that inhibits edema formation.

The basis for the selection of age 70 as the cut point for this analysis rests on a biological and clinical premise directly relevant to edema prevention trials. In large, prospective, population-based cohorts, brain atrophy is known to increase above the age of 70 years.⁹ Moreover, longitudinal studies using high-resolution magnetic resonance imaging have demonstrated an age-related decrease in total brain volume that seems to accelerate after 70 years of age.^{26–28} In patients with LHI, decreasing age is also a known predictor of the inability to tolerate the consequences of swelling.²⁹ Furthermore,

Table 1. Demographics and Baseline Characteristics in GAMES-RP Subjects Aged ≤ 70 Years

	IV Glyburide (n=35)	Placebo (n=30)	P Value
Demographics			
Age, y (SD)	55 (9)	60 (7)	0.017
Ethnicity			
Hispanic	2 (6%)	3 (10%)	0.65
Non-Hispanic	33 (94%)	27 (90%)	
Race			
White	30 (86%)	26 (87%)	1
Black	3 (9%)	2 (7%)	
Asian	2 (6%)	2 (7%)	
Stroke characteristics			
Cause of stroke			0.11
Large artery atherosclerosis	10 (29%)	7 (23%)	
Cardioaortic embolism	11 (31%)	16 (53%)	
Other	3 (9%)	4 (13%)	
Unknown	11 (31%)	3 (10%)	
Internal carotid artery occlusion	12 (34%)	11 (37%)	1
Left-sided infarction	18 (51%)	17 (57%)	0.80
Baseline NIHSS score	19 (16–22)	21 (16–23)	0.24
Baseline DWI, cm ³	164 (52)	167 (50)	0.83
Baseline blood glucose, mg/dL	120 (104–156)	123 (108–139)	1
Treatment			
Intravenous rTPA	21 (60%)	19 (63%)	0.80
Time intervals			
Time to rTPA, h	2.1 (1.0)	2.3 (1.1)	0.63
Time to MRI, h	6.0 (1.7)	5.8 (1.7)	0.72
Time to study drug, h	8.7 (1.3)	9.0 (1.3)	0.35

Data are mean (SD), mean (range), n (%), and median (IQR). DWI indicates diffusion-weighted imaging; GAMES-RP, Glyburide Advantage in Malignant Edema and Stroke—Remedy Pharmaceuticals; IQR, interquartile range; IV, intravenous; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health Stroke Scale; and rTPA, alteplase.

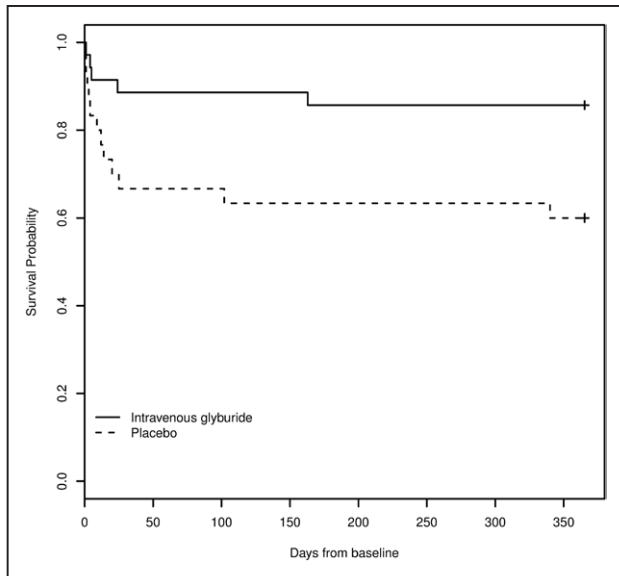


Figure 1. Kaplan–Meier survival curve for each treatment group.

Lee et al¹⁰ demonstrated that cerebral atrophy above a certain threshold (intercaudate distance, >20 mm) had an independent protective effect against brain herniation and the need for decompressive craniectomy, while simultaneously predicting poor functional outcome.³⁰ In addition, a recent study by Goto et al³¹ showed that elderly subjects with LHI required significantly larger infarct volumes to develop malignant edema and decreased level of consciousness when compared with subjects with lower age. Inclusion of brain atrophy as a marker of protective effect, in addition to the use of lesion volume as a prognostic factor, has led to more accurate prediction of a malignant course after LHI.³⁰ We measured baseline hemisphere volume in GAMES-RP, and the median hemisphere

volume in subjects >70 years of age was lower compared with subjects aged ≤70 years (492 versus 546 cm³; *P*=0.003).

Clinically, withdrawal of care is often the predominant mechanism of death in patients >70 years of age with acute brain injury.¹⁴ In patients with severe brain injury (eg, cardiac arrest or LHI), in which the severity of the initial insult is a strong predictor of outcome, withdrawal of care is especially common >70 years of age.¹⁵ Withdrawal of care is often because of disability related to the initial infarction or potentially undesirable procedures, such as placement of feeding tube or tracheostomy. Given the more prominent effects of cerebral edema in subjects ≤70 years of age, future investigations of efficacy of intravenous glyburide should focus on this population.

In GAMES-RP, we included established instruments to evaluate multiple dimensions of outcome after LHI. LHI is among the most devastating forms of arterial ischemic stroke with mortality rates as high as 50%.³² Although decompressive craniectomy has been shown to reduce death and, in selected subjects, improve outcomes, survivors often have severe disability and functional dependence.^{1,32,33} In addition to impaired motor function, these patients frequently experience injury to other domains, including cognition, language, and visual function, all of which significantly contribute to their overall outcomes.^{34–36} Many physicians, therefore, have concerns about the long-term quality of life among survivors of LHI.³⁷ Conversely, patients frequently achieve a satisfying level of psychological well being, despite their severe physical deficits.³⁵ Furthermore, van Middelaar et al³⁸ showed that patients who underwent surgical decompression for space-occupying middle cerebral artery infarction have a good mental quality of life that is comparable with the general population, and the majority of patients and caregivers would, in retrospect, again opt for surgery. We applied the EQ-5D and Barthel Index to

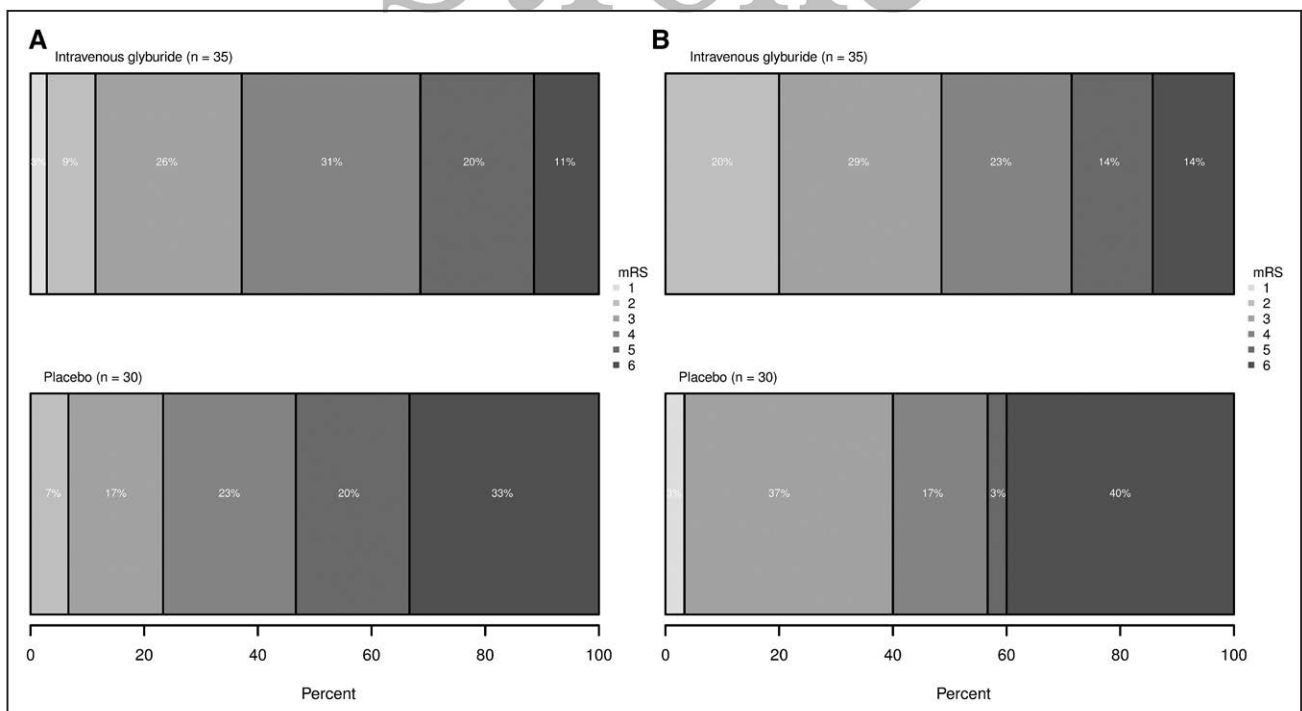


Figure 2. Functional outcomes on modified Rankin Scale (mRS) at 90 days (A) and 12 months (B) in subjects aged ≤70 years.

Table 2. Patient Outcomes

Outcome	Placebo (n=30)	IV Glyburide (n=35)	Effect Size (95% CI)	P Value
Mortality (%)				
90 d	10 (33%)	4 (11%)		
6 mo	11 (37%)	5 (14%)		
12 mo	12 (40%)	5 (14%)	HR, 0.34 (0.12–0.96)	0.042*
Barthel Index, mean (SD)				
90 d	34.5 (36.5)	50.7 (36.4)		
6 mo	39.5 (39.3)	54.4 (37.3)		
12 mo	39.5 (40.1)	60.1 (37.9)	20 (2.1–37)	0.029†
EQ-5D, mean (SD)				
90 d	0.29 (0.30)	0.43 (0.32)		
6 mo	0.33 (0.34)	0.49 (0.32)		
12 mo	0.33 (0.32)	0.49 (0.31)	0.154 (0.001–0.249)	0.048†

Data are n (%) and mean (SD). CI indicates confidence interval; EQ-5D, EuroQol group 5-dimension; GEE, generalized estimating equations; HR, hazard ratio; and IV, intravenous.

*P value is from a log-rank test.

†P value is from a linear, repeated measures GEE model for longitudinal outcomes.

assess 12-month quality of life and to explore whether or not patients with moderately severe disability have acceptable outcomes. The significant difference in the EQ-5D and Barthel Index observed in the present analysis suggests that these instruments provide additional important insights into overall quality of life after LHI, which is particularly important in the subgroup of patients with moderate-to-severe disability. However, after excluding patients who died, the treatment effect was no longer significant (Table 3)—a finding that suggests that the difference in Barthel Index and EQ-5D in this analysis was mainly determined by increased early mortality in the placebo group. The study was not powered for a quality of life end point, and it is possible that the sample size was too small to show a difference in quality of life among survivors of LHI. A multidimensional assessment of outcome should, therefore, be included in future investigations of efficacy to assess whether treatment with intravenous glyburide can, in addition to reducing mortality, lead to meaningful improvements in quality of life.

After the initial 90 days, we observed continued improvement ≤ 6 months, with moderate relative gains in recovery in both groups. Subsequently, outcomes remained stable to 12 months (Figure 3). These findings suggest that outcome at 90 days may inform longer term outcome and likely constitutes a meaningful end point for future studies of intravenous glyburide.

In this subgroup of patients ≤ 70 years of age, treatment with intravenous glyburide led to a 51% reduction in plasma MMP-9 levels, which is greater than the 39% reduction seen in the overall GAMES-RP cohort. MMP-9 is a marker of blood-brain barrier disruption and has been associated with cerebral edema after stroke.³⁹ MLS is another marker

Table 3. Barthel Index for Survivors (After Exclusion of Subjects Who Had Died)

Interval	Placebo		IV Glyburide		P Value
	n	Mean (SD)	n	Mean (SD)	
Barthel Index					
90 d	20	52 (33)	31	57 (33)	0.57*
6 mo	18	66 (29)	30	64 (32)	0.82*
12 mo	17	69 (27)	29	71 (31)	0.87*
Longitudinal GEE	Effect size (95% CI): IV glyburide–placebo				
	4.1 (–13 to 22)				0.64
EQ-5D					
90 d	19	0.44 (0.26)	30	0.49 (0.29)	0.54*
6 mo	18	0.54 (0.29)	29	0.58 (0.26)	0.66*
12 mo	17	0.57 (0.22)	29	0.57 (0.26)	0.92*
Longitudinal GEE	Effect size (95% CI): IV glyburide–placebo				
	0.024 (–0.12 to 0.16)				0.74†

EQ-5D for survivors (after exclusion of subjects who had died). Imputation with 0 for death has not been applied. CI indicates confidence interval; EQ-5D, EuroQol group 5-dimension; GEE, generalized estimating equations; and IV, intravenous.

*P value from a *t* test for each interval.

†P value is from Wald test for GEE with adjustment for age.

for cerebral edema after LHI. The extent of lateral displacement of midline structures has been correlated with decreased level of consciousness⁴⁰—a finding that was also seen in GAMES-RP.⁸ The significant reduction in MLS in patients treated with intravenous glyburide further supports the potential positive effect of this therapy on cerebral edema in patients ≤ 70 years of age.

A notable strength of our study is prospective data collection using standardized methods that address multiple domains, all at multiple time points. However, our study has important limitations. First, this study was an exploratory, post hoc subgroup analysis of the GAMES-RP trial. A significant imbalance in age could have favored the intravenous glyburide group. The small sample that results from any age cut point limits the power of an exploratory analysis. These results are hypothesis generating. Also, although there was no significant difference in the rate of decompressive craniectomy between treatment groups, there was a 10% increase in the glyburide group. Alternatively, as a postrandomization practice variable, it is also possible that decompressive craniectomy was performed in an inconsistent manner, favoring those patients most likely to benefit. Whereas decompressive craniectomy may improve outcome, craniectomy plus subsequent cranioplasty necessitates recovery from 2 surgeries, both of which expose patients to complications that can negatively impact outcome.

Clinical studies designed to detect an effect of a treatment that inhibits edema formation may consider enriching the population with patients ≤ 70 years of age. Although the present analyses are exploratory, the 12-month effects of glyburide on mortality provide evidence for a potential role in improving outcomes in patients with large hemispheric stroke. The results support additional study and prospective

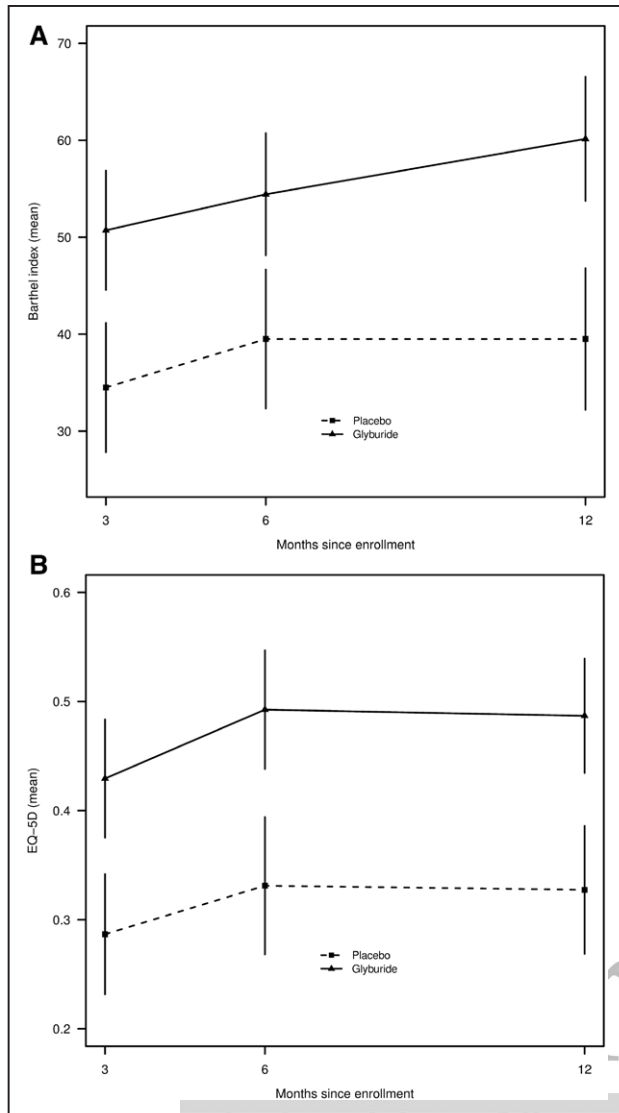


Figure 3. Barthelemy Index (A) and EuroQol group 5-dimension (EQ-5D; B) at 90 days, 6 months, and 12 months. Vertical bars represent mean \pm SE.

trials designed to assess the role of intravenous glyburide, or BIIB093, for improving outcomes for patients with LHI.

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Disclosures

Dr Simard has a patent related to the study and has shares in Remedy Pharmaceuticals. Drs Kimberly, Sheth, Elm, and Sze and Laboratory received grants from Remedy Pharmaceuticals during the conduct of this study. Drs Sheth and Kimberly also receive research grants from the American Heart Association. Drs Molyneaux and Hinson received grants from Remedy Pharmaceuticals outside of the submitted work.

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References

- Vahedi K, Hofmeijer J, Juettler E, Vicaut E, George B, Algra A, et al; DECIMAL, DESTINY, and HAMLET Investigators. Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomised controlled trials. *Lancet Neurol*. 2007;6:215–222. doi: 10.1016/S1474-4422(07)70036-4.
- Wijdicks EF, Sheth KN, Carter BS, Greer DM, Kasner SE, Kimberly WT, et al; American Heart Association Stroke Council. Recommendations for the management of cerebral and cerebellar infarction with swelling: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45:1222–1238. doi: 10.1161/01.str.0000441965.15164.d6.
- Hofmeijer J, van der Worp HB, Kappelle LJ. Treatment of space-occupying cerebral infarction. *Crit Care Med*. 2003;31:617–625. doi: 10.1097/01.CCM.0000050446.16158.80.
- Huttner HB, Schwab S. Malignant middle cerebral artery infarction: clinical characteristics, treatment strategies, and future perspectives. *Lancet Neurol*. 2009;8:949–958. doi: 10.1016/S1474-4422(09)70224-8.
- Kurland DB, Khaladj-Ghom A, Stokum JA, Carusillo B, Karimy JK, Gerzanich V, et al. Complications associated with decompressive craniectomy: a systematic review. *Neurocrit Care*. 2015;23:292–304. doi: 10.1007/s12028-015-0144-7.
- Simard JM, Woo SK, Schwartzbauer GT, Gerzanich V. Sulfonylurea receptor 1 in central nervous system injury: a focused review. *J Cereb Blood Flow Metab*. 2012;32:1699–1717. doi: 10.1038/jcbfm.2012.91.
- Simard JM, Sheth KN, Kimberly WT, Stern BJ, del Zoppo GJ, Jacobson S, et al. Glibenclamide in cerebral ischemia and stroke. *Neurocrit Care*. 2014;20:319–333. doi: 10.1007/s12028-013-9923-1.
- Sheth KN, Elm JJ, Molyneaux BJ, Hinson H, Beslow LA, Sze GK, et al. Safety and efficacy of intravenous glyburide on brain swelling after large hemispheric infarction (GAMES-RP): a randomised, double-blind, placebo-controlled phase 2 trial. *Lancet Neurol*. 2016;15:1160–1169. doi: 10.1016/S1474-4422(16)30196-X.
- DeCarli C, Massaro J, Harvey D, Hald J, Tullberg M, Au R, et al. Measures of brain morphology and infarction in the framingham heart study: establishing what is normal. *Neurobiol Aging*. 2005;26:491–510. doi: 10.1016/j.neurobiolaging.2004.05.004.
- Lee SH, Oh CW, Han JH, Kim CY, Kwon OK, Son YJ, et al. The effect of brain atrophy on outcome after a large cerebral infarction. *J Neurol Neurosurg Psychiatry*. 2010;81:1316–1321. doi: 10.1136/jnnp.2009.197335.
- Krieger DW, Demchuk AM, Kasner SE, Jauss M, Hantson L. Early clinical and radiological predictors of fatal brain swelling in ischemic stroke. *Stroke*. 1999;30:287–292.
- Jaramillo A, Góngora-Rivera F, Labreuche J, Hauw JJ, Amarenco P. Predictors for malignant middle cerebral artery infarctions: a postmortem analysis. *Neurology*. 2006;66:815–820. doi: 10.1212/01.wnl.0000203649.60211.0e.
- Oppenheim C, Samson Y, Manai R, Lalam T, Vandamme X, Crozier S, et al. Prediction of malignant middle cerebral artery infarction by diffusion-weighted imaging. *Stroke*. 2000;31:2175–2181.
- Holloway RG, Arnold RM, Creutzfeldt CJ, Lewis EF, Lutz BJ, McCann RM, et al; American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology. Palliative and end-of-life care in stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45:1887–1916. doi: 10.1161/STR.0000000000000015.
- Albaeni A, Chandra-Strobus N, Vaidya D, Eid SM. Predictors of early care withdrawal following out-of-hospital cardiac arrest. *Resuscitation*. 2014;85:1455–1461. doi: 10.1016/j.resuscitation.2014.08.030.
- Sheth KN, Elm JJ, Beslow LA, Sze GK, Kimberly WT. Glyburide Advantage in Malignant Edema and Stroke (GAMES-RP) trial: rationale and design. *Neurocrit Care*. 2016;24:132–139. doi: 10.1007/s12028-015-0189-7.
- Sulter G, Steen C, De Keyser J. Use of the Barthelemy index and modified Rankin scale in acute stroke trials. *Stroke*. 1999;30:1538–1541.
- van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke*. 1988;19:604–607.
- Mahoney FI, Barthel DW. Functional evaluation: the barthelemy index. *Md State Med J*. 1965;14:61–65.

20. Kasner SE. Clinical interpretation and use of stroke scales. *Lancet Neurol*. 2006;5:603–612. doi: 10.1016/S1474-4422(06)70495-1.
21. Dorman PJ, Waddell F, Slattery J, Dennis M, Sandcock P. Is the EuroQol a valid measure of health-related quality of life after stroke? *Stroke*. 1997;28:1876–1882.
22. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. *Ann Med*. 2001;33:337–343.
23. Luo N, Johnson JA, Shaw JW, Feeny D, Coons SJ. Self-reported health status of the general adult U.S. population as assessed by the EQ-5D and health utilities index. *Med Care*. 2005;43:1078–1086.
24. Shaw JW, Johnson JA, Coons SJ. US valuation of the EQ-5D health states: development and testing of the D1 valuation model. *Med Care*. 2005;43:203–220.
25. Yan J, Fine J. Estimating equations for association structures. *Stat Med*. 2004;23:859–874; discussion 875. doi: 10.1002/sim.1650.
26. Fox NC, Schott JM. Imaging cerebral atrophy: normal ageing to Alzheimer's disease. *Lancet*. 2004;363:392–394. doi: 10.1016/S0140-6736(04)15441-X.
27. Scallan RI, Frost C, Jenkins R, Whitwell JL, Rossor MN, Fox NC. A longitudinal study of brain volume changes in normal aging using serial registered magnetic resonance imaging. *Arch Neurol*. 2003;60:989–994. doi: 10.1001/archneur.60.7.989.
28. Resnick SM, Pham DL, Kraut MA, Zonderman AB, Davatzikos C. Longitudinal magnetic resonance imaging studies of older adults: a shrinking brain. *J Neurosci*. 2003;23:3295–3301.
29. Thomalla G, Hartmann F, Juettler E, Singer OC, Lehnhardt FG, Köhrmann M, et al; Clinical Trial Net of the German Competence Network Stroke. Prediction of malignant middle cerebral artery infarction by magnetic resonance imaging within 6 hours of symptom onset: a prospective multicenter observational study. *Ann Neurol*. 2010;68:435–445. doi: 10.1002/ana.22125.
30. Beck C, Krutzelmann A, Forkert ND, Juettler E, Singer OC, Köhrmann M, et al. A simple brain atrophy measure improves the prediction of malignant middle cerebral artery infarction by acute DWI lesion volume. *J Neurol*. 2014;261:1097–1103. doi: 10.1007/s00415-014-7324-9.
31. Goto Y, Kumura E, Watabe T, Nakamura H, Nishino A, Koyama T, et al. Prediction of malignant middle cerebral artery infarction in elderly patients. *J Stroke Cerebrovasc Dis*. 2016;25:1389–1395. doi: 10.1016/j.jstrokecerebrovasdis.2015.12.034.
32. Alexander P, Heels-Ansdell D, Siemieniuk R, Bhatnagar N, Chang Y, Fei Y, et al. Hemicraniectomy versus medical treatment with large MCA infarct: a review and meta-analysis. *BMJ Open*. 2016;6:e014390. doi: 10.1136/bmjopen-2016-014390.
33. Rahme R, Zuccarello M, Kleindorfer D, Adeoye OM, Ringer AJ. Decompressive hemicraniectomy for malignant middle cerebral artery territory infarction: is life worth living? *J Neurosurg*. 2012;117:749–754. doi: 10.3171/2012.6.JNS111140.
34. Geurts M, van der Worp HB, Kappelle LJ, Amelink GJ, Algra A, Hofmeijer J; HAMLET Steering Committee. Surgical decompression for space-occupying cerebral infarction: outcomes at 3 years in the randomized HAMLET trial. *Stroke*. 2013;44:2506–2508. doi: 10.1161/STROKEAHA.113.002014.
35. von Sarnowski B, Kleist-Welch Guerra W, Kohlmann T, Moock J, Khaw AV, Kessler C, et al. Long-term health-related quality of life after decompressive hemicraniectomy in stroke patients with life-threatening space-occupying brain edema. *Clin Neurol Neurosurg*. 2012;114:627–633. doi: 10.1016/j.clineuro.2011.12.026.
36. Hofmeijer J, van der Worp HB, Kappelle LJ, Amelink GJ, Algra A, van Zandvoort MJ. Cognitive outcome of survivors of space-occupying hemispheric infarction. *J Neurol*. 2013;260:1396–1403. doi: 10.1007/s00415-012-6810-1.
37. Schwarz S, Kühner C. Prognosis and quality of life after decompressive hemicraniectomy: a nationwide survey in Germany on the attitudes held by doctors and nurses. *Nervenarzt*. 2012;83:731–740. doi: 10.1007/s00115-011-3402-8.
38. van Middelaar T, Richard E, van der Worp HB, van den Munkhof P, Nieuwkerk PT, Visser MC, et al. Quality of life after surgical decompression for a space-occupying middle cerebral artery infarct: a cohort study. *BMC Neurol*. 2015;15:156. doi: 10.1186/s12883-015-0407-0.
39. Serena J, Blanco M, Castellanos M, Silva Y, Vivancos J, Moro MA, et al. The prediction of malignant cerebral infarction by molecular brain barrier disruption markers. *Stroke*. 2005;36:1921–1926. doi: 10.1161/01.STR.0000177870.14967.94.
40. Ropper AH. Lateral displacement of the brain and level of consciousness in patients with an acute hemispherical mass. *N Engl J Med*. 1986;314:953–958. doi: 10.1056/NEJM198604103141504.

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