Stroke outcome related to initial volume status and diuretic use

Renner CJ,[1] Kasner SE,[1] Bath PM,[2] Bahouth MN[3] on behalf of the VISTA Acute Steering Committee

1- University of Pennsylvania, Philadelphia, PA, USA
2- Stroke Trials Unit, University of Nottingham, Nottingham, Notts, U.K.
3- Johns Hopkins School of Medicine, Baltimore, MD, USA

Word Count:

Abstract: 241
Manuscript: 2883

Tables: 4
Figures: 2
Appendix (supplemental data): 1

Statistical analysis completed by Dr Scott Kasner

Correspondence:

Mona N. Bahouth, MD, PhD
Assistant Professor of Neurology
Johns Hopkins School of Medicine
600 N Wolfe St; Phipps 486
Baltimore, Maryland 21287
Email: mbahout1@jhmi.edu
Twitter handle: @MonaBahouth

Nonstandard Abbreviations and Acronyms:

ENOS: Efficacy of nitric oxide trial

mRS: Modified Rankin scale score

rtPA: Tissue plasminogen activator

THRIVE: Totaled Health Risks in Vascular Events Score

VCS: Volume contracted state

VISTA: Virtual International Stroke Trials Archive

Abstract

Background: We hypothesized that stroke outcome is related to multiple baseline hydration-related factors including volume contracted state (VCS) and diuretic use.

Methods: We analyzed a prospective cohort of subjects with ischemic stroke <24 hours of onset, enrolled in acute treatment trials within the Virtual International Stroke Trials Archive. A VCS was defined based on BUN-to-creatinine ratio. The primary endpoint was modified Rankin Scale (mRS) at 90 days. Primary analysis employed generalized ordinal logistic regression over the mRS range, adjusted for THRIVE score, onset-to-enrollment time, and thrombolytic usage.

Results: Of 5971 eligible stroke patients, 42% were taking diuretics at the time of hospitalization and 44% were in a VCS. Patients with VCS were older, had more vascular risk factors, were more likely taking diuretics and had more severe strokes. Diuretic use was associated with both reduced chance of achieving a good functional outcome (OR 0.57;95%CI 0.52-0.63) and increased mortality at 90 days (OR 2.30;95%CI 2.04-2.61). VCS was associated with greater mortality 90 days post-stroke (OR 1.53;95%CI 1.33-1.76). There was no evidence of effect modification among the three exposures of VCS, diuretic use, or hypokalemia in relation to outcome.

Conclusions: A VCS at the time of hospitalization was associated with more severe stroke and odds of death but not associated with worse functional outcome when accounting for relevant characteristics. Diuretic use and low serum potassium at the time of stroke onset were associated with worse outcome and may be worthy of further investigation.

Key words: hydration, diuretic, acute stroke, stroke

Introduction

The pathophysiology of acute ischemic stroke depends upon the complex interactions among cerebral and systemic hemodynamic parameters. Previous studies have suggested that the use of diuretics and other antihypertensive medications may reduce the risk of, reduce severity of, and improve outcome after stroke [1-3]. However, these medications have the potential to increase the likelihood of dehydration, or more accurately a volume contracted state (VCS) at the time of stroke which may worsen functional outcome [4]. A common side effect of these medications is also change in electrolytes, most notably depletion of serum potassium which may also be associated with risk of stroke and stroke-related death [5-7]. Whether diuretics, hydration status, and potassium levels have an effect in the acute setting has not been determined.

In the acute setting, ischemic stroke patients are commonly administered intravenous fluid under the premise that dehydration can lead to reduced cerebral perfusion, and ultimately worse clinical outcome [4,8,9]. Indeed, the 2018 AHA/ASA guidelines for early management of patients with acute ischemic stroke merely state that, “Hypotension and hypovolemia should be corrected to maintain systemic perfusion levels necessary to support organ function” with an admission that, “There are no data to guide volume and duration of parenteral fluid delivery” [10]. While the class of recommendation for this guideline is 1 (strong), the evidence for this merely comes from consensus of expert opinion based on clinical experience. Surprisingly, data regarding the hydration practices and efficacy of this practice are sparse [11,12]. A few studies have recently begun to look at the effect of a volume contracted state (VCS) in acute stroke patients on post-stroke outcomes [13-16]. A single-center study found that those in VCS had worse clinical outcome at 90 days than those who were euvolemic [16]. A recent substudy of the ENOS (efficacy of nitric oxide) trial involving data from 310 participants found an unfavorable shift in the Modified Rankin Scale (mRS) and increased death at day 90 in patients with increased urea, however other markers of dehydration did not yield consistent findings [17].

The Virtual International Stroke Trials Archive (VISTA) is a combined resource that includes data contributed by principal investigators of numerous international acute stroke trials [18]. It has been anonymized with the goal of providing a large and centrally collated data set for investigators wishing to perform exploratory analyses. All included patients had baseline assessment within 24 hours from stroke onset and confirmed stroke diagnosis using cerebral imaging. We use this cohort to investigate the relationship between diuretic use, the

consequences of diuretic use at the time of stroke including hypokalemia and volume contraction, and association with stroke outcome.

We aimed to investigate the potential consequences of diuretic use and the associations among these factors with outcome after acute ischemic stroke in an international multicenter database. We hypothesized that patients on diuretics and in a VCS would have worse functional outcomes at 90 days than those who were euvolemic upon arrival to the hospital.

Methods

We conducted a cohort study of patients who were prospectively enrolled in clinical trials within the Virtual International Stroke Trials Archive (VISTA) [18]. Patients were included if they had an ischemic stroke diagnosis within 24 hours of onset or time last known to be normal. There was no limitation to NIH Stroke Scale (NIHSS) score for inclusion in this archive. Patients were excluded if their stroke was due to a primary intracranial hemorrhage and/or if they were undergoing dialysis prior to the stroke admission. To be included in this analysis, subjects were additionally required to have the following data available: mRS at 90 days, NIHSS score at baseline and at 90 days, time from stroke onset, whether or not they received intravenous thrombolysis (rtPA), baseline medications (e.g. diuretic), and medical history including hypertension, atrial fibrillation, and diabetes mellitus. In all the VISTA trials included, mRS was expected to be measured in person around 90 days as one of the key outcomes. As VISTA is a conglomerate of trials, each trial had its own allowances for the time window around 90 days, the use of telephone mRS for patients unable to be evaluated in person, and information carried forward from prior visits if needed.

VCS was defined a priori as a BUN-to-creatinine ratio of >20 (urea:Cr >100) as has previously been defined, and is referred to here as VCS-20 [17]. We additionally conducted similar analysis using a post hoc definition of BUN-to-creatinine ratio>30 (urea:Cr > 150), referred to as VCS-30. All baseline lab values were measured prior to randomization in each of the individual trials, typically upon arrival to the hospital at the time of stroke. Estimated glomerular filtration rate (eGFR) was calculated based on age, sex, race, and initial serum creatinine, and then chronic kidney disease stage was determined. All included patients were from sites with institutional review board approval for study enrollment. Data for this study are hosted by the

Virtual Trials Archives (http://www.virtualtrialsarchives.org). Because the data collected for this study contain human subjects information, reasonable requests to access the dataset from qualified researchers trained in human subject confidentiality protocols may be sent to vista.coordinator@glasgow.ac.uk.

Statistical Analyses

Baseline characteristics of subjects with and without VCS were compared using student's t test for continuous variables, chi-squared test for categorical variables, and Wilcoxon rank-sum test for ordinal variables. The primary endpoint was functional outcome at 90 days, as measured by the Modified Rankin Scale (mRS). The mRS ranges from 0 (completely normal) to 5 (severely disabled and dependent), and 6 is assigned if the patient died. Generalized ordinal logistic regression was performed over the full range of mRS scores, comparing these outcomes between VCS and euvolemic patients in univariate analysis. For the multivariable analyses, we calculated the THRIVE score which includes age, baseline NIHSS score, hypertension, diabetes, and atrial fibrillation to minimize the number of covariates used in the models [19]. We pre-specified adjustment for the THRIVE score, onset-to-enrollment time, and intravenous rtPA usage. Stratified analyses and tests for interaction were performed based on use of diuretics prior to stroke and thrombolysis for the event. Secondary analyses of the primary endpoint were a comparison of the proportion of patients with a bad outcome, defined as mRS> 2 at 90 days, with similar adjustments and stratifications as above. We also assessed change in NIHSS score from baseline to day 90 and mortality by day 90 as secondary endpoints. All analyses were performed using Stata/SE 12.1 (StataCorp, College Station, TX).

Results

The VISTA database yielded 7444 patients who met the eligibility criteria for this analysis, with 3051/7444 (41%) of this subset prescribed diuretics at the time of hospital presentation. Of this group, 5971 (80%) had sufficient laboratory testing to measure baseline VCS. Forty-four percent (2626/5971) demonstrated VCS-20. Patients in VCS-20 were older, more often female, and had higher NIHSS scores (Table 1). They were also more likely to have hypertension, diabetes, atrial fibrillation, and CHF. THRIVE score was higher in the VCS-20 group, indicating a higher risk for worse outcome. Patients in VCS-20 were more likely to be taking diuretics. There was

no difference in stroke onset-to-enrollment time and use of intravenous thrombolysis between both groups. Of the 6833 patients with available serum potassium data, 624 (9.1%) had low serum potassium levels (<3.5 mmol/L) while 344 (5.0%) had high serum potassium (≥5.0 mmol/L). Using the VCS-30 definition yielded similar outcomes (see Appendix 1).

In the final cohort of acute stroke patients, 3051/5971 (51%) were prescribed diuretic medications. Diuretic use was associated with greater odds of achieving a worse outcome after 90 days post-stroke in both unadjusted and adjusted models (OR 1.31; 95% CI 1.20-1.42; p< 0.001). There was also a significantly increased odds of death for patients who were prescribed diuretics at the time of stroke as compared with those who were not, even after adjustment (adjusted OR 1.64; 95% CI 1.44-1.88; p<0.001). See Table 2. The adverse relationship was driven predominantly by the 2988/3051 (98%) of patients prescribed non-potassium-sparing diuretics at the time of hospitalization (Table 2). Change in NIHSS from baseline to day 90 was not different when comparing patients who were taking and those who were not taking diuretic medications. Patients prescribed diuretics were more likely to be in a VCS as compared with those who were not (p<0.001). There was no evidence of effect modification (statistical treatment interaction) between VCS and diuretic use in either VCS-20 or VCS-30 groups ($p_{interaction}$=0.997 and $p_{interaction}$=0.536, respectively).

In this cohort, 2626/5971 (44%) presented to the hospital in a volume contracted state as defined by BUN/creatinine ratio > 20). VCS-20 also appeared to be associated with an adverse shift in mRS scores, worse outcome, and higher mortality compared to those without VCS-20 in crude analyses (Table 3). After adjustment for THRIVE scores, onset to treatment time, and the use of thrombolysis, the effects on mRS scores were no longer evident. Change in NIHSS from baseline to day 90 was not different between groups when comparing patients with and without VCS-20. VCS-20 was associated with 1.18 adjusted odds of death at 90 days (aOR 1.01-1.31; p=0.032). There was no evidence of effect modification on functional outcome (mRS) between VCS-20 and diuretic use ($p_{interaction}$=0.940). The distribution of predicted 90-day mRS scores after adjustment in relation to initial volume status are shown in Figures 1 (VCS-20) and Figure 2 (VCS-30). In a sensitivity analysis, we adjusted our model for the individual components of THRIVE rather than the summary score, which yielded similar results. Analyses using the post-hoc VCS-30 definition yielded similar magnitudes of the associations for the mRS, NIHSS score, and mortality, though the latter was no longer significant (Table 3).

In this group 969/5971(16%) demonstrated an abnormality in serum potassium at the time of hospital presentation for stroke. Low potassium at baseline was not associated with change in NIHSS scores, a shift in mRS scores, or mortality. Elevated potassium appeared to be associated with an adverse shift in mRS scores and higher mortality compared to euvolemia in crude analyses, but not after adjustment (Table 4). There was no evidence of effect modification on functional outcome (mRS) between VCS-20 and low potassium level ($p_{interaction}$=0.492).

Discussion

We found that patients with VCS had increased adjusted odds of death after 90 days as compared with patients who did not have VCS. Further, more patients who were prescribed diuretics were in a VCS and diuretic use appear to be associated with worse functional outcome and higher odds of death after adjustment for age, stroke severity and comorbid conditions known to worsen stroke outcome. Taken together, these findings suggest additional physiologically relevant and potentially modifiable variables to predict and influence stroke outcome. There is a paucity of data about the relationship between a VCS and stroke outcome and this is the first attempt to analyze the relationship diuretic use and the relationship to functional outcome in a large group of prospectively recruited acute stroke patients from a group of international stroke study sites.

These data are consistent with the frequency of volume contracted state seen in single site, observational studies [4,20,21]. VCS is more common in older patients with more comorbidities and more severe strokes. After adjusting for these variables, we found that patients in volume contracted state, did not have worse outcomes at 90 days compared to those who were euvolemic on arrival to the hospital, but appeared to have increased mortality. Prior studies have reported that VCS negatively affects outcome after acute ischemic stroke but may have had limited power to account for confounding by other clinical factors [13-16]. Our study improves upon the limitations of these studies by expanding the sample size to include subjects from a large database of stroke clinical trials with systematic assessments of outcomes, enhancing the reliability and precision of the results. Similarly, investigators from the ENOS trial found no evidence of a consistent relationship between markers of VCS and outcome. Together, these results suggest that these biochemical indicators of dehydration do not adequately reflect tissue perfusion or that any effect of volume status on perfusion is small compared to other factors such as arterial recanalization.

We also observed a relationship between prescribed diuretic use prior to stroke admission and poor stroke outcome. This result seems to be mainly driven by the majority subgroup of patients on non-K-sparing diuretics. This effect was independent from volume status. A prior report from a single center cohort suggested that diuretics, especially thiazide diuretics may improve early outcome after stroke [22]. Our observation that diuretic use by itself is associated with worse outcome may be potentially attributed the underlying comorbid conditions or provider concern that administration of intravenous fluids could contribute to decompensated heart failure resulting in a more prolonged volume contracted state. We do not have data specific to the frequency or rate of treatment of the VCS to validate this hypothesis and could be an interesting focus of future study. Prior studies have shown a strong association between diuretic use and dehydration in stroke patients [9,23]. Moreover, given our finding that fewer good outcomes resulted from low serum potassium, it is conceivable that a potassium-lowering medication would negatively affect outcome through this indirect route. In a similar vein, potassium-sparing diuretics might indirectly affect outcome by preserving serum potassium levels.

Hypokalemia is another potentially modifiable parameter in patients presenting to the hospital with acute stroke, with a previously proposed mechanism involving adrenaline-induced hypokalemia [24]. Previous studies have suggested that hypokalemia may lead to worse clinical outcome after stroke [25,26]. Our hypothesis that acute ischemic stroke patients with low serum potassium at presentation will have worse clinical outcome at 90 days yielded mixed results, with no shift across the mRS scale but fewer good outcomes when dichotomized. This finding may be spurious due to multiple testing but should be evaluated in an independent dataset. While VCS, diuretic use, and low potassium are likely to be overlapping conditions, there did not appear to be any interactions among their relationships with clinical outcomes.

These findings are clinically important, though there were some notable limitations in our study. First, this was a retrospective analysis of prospective cohorts, therefore we were limited to the data available in the VISTA database, i.e., stroke trial data, each with specific eligibility criteria. This introduces the possibility of selection bias as a significant limitation. Notably, few patients likely received thrombectomy as it was not the standard of care when these trials were completed. Additionally, though patients were prescribed diuretics, we do not have any information about adherence with these medications. Next, the data for potentially relevant variables such as urine specific gravity, urine sodium, serum bicarbonate, measured osmolality,

and ejection fraction are not routinely collected in stroke trials and therefore were not included in the analysis. Using a single measure at baseline likely does not fully reflect the dynamic situation of a patient with an acute ischemic stroke. We additionally acknowledge that this cohort enrolled patients with more severe and thus threaten the generalizability of these data to those with mild stroke. There are likely numerous unmeasured residual confounders and both hypokalemia and VCS-20 may simply reflect a marker of a sicker cohort of stroke patients.

To untangle these phenomena, we utilized this commonly collected biomarker. Given that most stroke trials routinely collected BUN or urea and creatinine, we used BUN-creatinine ratio as a proxy for volume status and found that BUN-creatinine ratio>20, as has been used previously, defines about half of subjects as VCS [17]. This finding suggests that either VCS is extremely common, or the definition is too imprecise, likely including other etiologies of elevated BUN/creatinine ratio such as GI bleeding or steroid use. This is a significant limitation to interpreting these results and underscores the issue with not having a gold standard, objective definition for VCS. Other studies have defined VCS as BUN-creatinine ratio>15 given that this ratio is frequently thought to indicate azotemia and dehydration [14-16, 27, 28]. Had we used this definition in this study, 78% of subjects would have been defined as VCS. We also evaluated a more stringent ratio of 30, present in about 8% of patients, with largely similar results.

Despite these limitations this is an important study to assist in understanding the complex relationship between hydration status and clinical outcome after stroke. For the majority of stroke patients, avoiding metabolic complications in the early stroke period is the primary approach to improving patient outcomes. This cohort of patients takes an important next step in exploring possible mechanisms and begin developing clinical protocols to modify relevant variables. It is the first analysis of a cohort of international patients with prospective and hyperacute data. It is a large sample size with a standardized and monitored data collection methodology. Investigators were blinded to the hypothesis of this study and therefore hydration practices were likely consistent with “real world” practices which are useful to clinicians who are treating similar patients around the world. While these results cannot directly support a change in clinical practice related to re-hydration after stroke, it provides critical foundational information to better understanding these associations.

Conclusions

Volume contracted state is associated with increased odds of death in this cohort of patients with acute ischemic stroke. Acute ischemic stroke patients taking diuretics and possibly those with low serum potassium appear to be associated with worse outcome. Future study should investigate stroke patient practices related to these clinically important variables.

Acknowledgments and Sources of Funding:

Drs. Renner and Kasner were supported by NIH grants U10NS086474 and U24NS107224;

Dr. Bath is Stroke Association Professor of Stroke Medicine and Emeritus NIHR Senior Investigator;

Dr. Bahouth is supported by the American Heart Association 18CDA34110126

Disclosures:

The authors have no competing interests to declare that are relevant to the content of this article.

References

1. Psaty BM, Smith NL, Siscovick DS, Koepsell, TD, Weiss, NS, Heckbert, SR, Lemaitre, RN, Wagner, EH, Furberg, CD. Health outcomes associated with antihypertensive therapies used as first-line agents. A systematic review and meta-analysis. *JAMA.* 1997;277:739–745.
2. Tziomalos K, Giampatzis V, Bouziana SD, Spanou M, Papadopoulou, M, Kazantzidou, P, Kostaki, Kouparanis, A, Savopoulos, C, Hatzitolios, AI. Effects of different classes of antihypertensive agents on the outcome of acute ischemic stroke. *J Clin Hypertens.* (Greenwich). 2015;17(4):275-80.
3. Shih HM, Lin WC, Wang CH, Lin LC. Hypertensive patients using thiazide diuretics as primary stroke prevention make better functional outcome after ischemic stroke. *J Stroke Cerebrovasc Dis*. 2014;23(9):2414-8.
4. Schrock, JW, Glasenapp, M, & Drogell, K. Elevated blood urea nitrogen/creatinine ratio is associated with poor outcome in patients with ischemic stroke. *Clinical Neurology and Neurosurgery.* 2012*;114*(7):881-884.
5. Green, D., Ropper, A., Kronmal, R., Psaty, B., & Burke, G. (n.d.). Serum potassium level and dietary potassium intake as risk factors for stroke. *Neurology*. 59(3):314–320.
6. Khaw K, Barrett-Connor E. Dietary potassium and stroke associated mortality: a 12-year prospective population study. *N Engl J Med*. 1987;316:235–240.
7. Gao F, Wang CT, Chen C, Guo X, Yang LH, Ma XC, Han JF. Effect of Hypokalemia on Functional Outcome at 3 Months Post-Stroke Among First-Ever Acute Ischemic Stroke Patients. *Med Sci Monit*. 2017;10(23):2825-2832.
8. Owens WB. Blood pressure control in acute cerebrovascular disease. *J Clin Hypertens* 2011;13:205–11.
9. Rowat A, Graham C, Dennis M. Dehydration in hospital-admitted stroke patients. *Stroke.* 2012;43:857–9.
10. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller, J, Brown, M, Demaerschalk, BM, Hoh, B, et al. 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2018;49:e46–e110.
11. Visvanathan A, Dennis M, Whiteley W. Parenteral fluid regimens for improving functional outcome in people with acute stroke. *Cochrane Database Syst Rev*. 2015:CD011138.
12. Bahouth, MN, Gottesmam, RF, Szanton, SL. Primary 'dehydration' and acute stroke: a systematic research review. *J Neurology*. 2018;265(10):2167-2181.
13. Rowat A, Graham, C, Dennis, M. Dehydration in hospital admitted stroke patients: detection, frequency and association. *Stroke*. 2012;43:857-859.
14. Lin LC, Yang, JT, Weng, HH, Hsiao, CT, Lai, SL, Fann, WC. Predictors of early clinical deterioration after acute ischemic stroke. *American J Emerg Med*. 2011;29(6):577-581.
15. Lin, CJ, Yang, JT, Huang, YC, Tsai, YN, Lee, MH, Lee, M, Hsiao, CT, Hsaio, KY, Lin, LC. Favorable outcome of blood urea nitrogen/creatinine-based hydration therapy 3 months after acute ischemic stroke. *The American Journal of Emergency Medicine***.** 2016*;34*(12):2414-2418.
16. Bahouth MN, Gaddis A, Hillis AE, Gottesman RF. Pilot study of volume contracted state and hospital outcome after stroke. *Neurol Clin Pract*. 2018;8(1)21-26.
17. Billington CK, Appleton JP, Berge E, Sprigg N, Glover M, Bath, PMW. Impact of hydration status on haemodynamics, effects of acute blood pressure-lowering treatment, and prognosis after stroke. *Br J Clin Pharmacol*. 2018;84:2914-2922.
18. Ali, M, Bath, PMW, Curram, J, Davis, SM, Diener, HC, Donnan, GA, Fisher, M, Gregson, BA, Grotta, J, Hacke, W, et al. The Virtual International Stroke Trials Archive. *Stroke*. 2007;38:1905-1910

19. Flint AC, Cullen SP, Faigeles BS, Rao VA. Predicting Long-Term Outcome after Endovascular Stroke Treatment: The Totaled Health Risks in Vascular Events Score. *Am J Neuroradio*l. 2010;7:1192-1196.
20. Rodriguez GJ, Cordina SM, Vazquez G, Suri MF, Kirmani JF, Ezzeddine MA, Qureshi, AI. The hydration influence on the risk of stroke (THIRST) study. *Neurocrit Care*. 2009;10(2):187–94.
21. Miller JB, Lee A, Siszanski JP, Tustian M, Corcoran JL, Moore S, Rodriguez L, Lewandowski CA. Challenge of intravascular volume assessment in acute ischemic stroke. *Am J Emerg Med*. 2018;36(6):1018-1021.
22. Wright JM, Musini VM. First-line drugs for hypertension. *Cochrane Database Syst Rev.* 2009:CD001841.
23. Churchill M, Grimm S, Reding M. Risks of diuretic usage following stroke. *Neurorehabil Neural Repair*. 2004;18:161–165.
24. Gariballa SE, Robinson TG, Fotherby MD. Hypokalemia and potassium excretion in stroke patients. *J Am Geriatr Soc.* 1997;45:1454-1458.
25. Khaw K, Barrett-Connor E. Dietary potassium and stroke associated mortality: a 12-year prospective population study. *N Engl J Med*. 1987;316:235–240.
26. Gao F, Wang CT, Chen C, Guo X, Yang LH, Ma XC, Han JF. Effect of Hypokalemia on Functional Outcome at 3 Months Post-Stroke Among First-Ever Acute Ischemic Stroke Patients. *Med Sci Monit*. 2017;23:2825-2832.
27. Liu CH, Lin SC, Lin JR, Yang JT, Chang YJ, Chang CH, Chang, TY, Huang, KL, Ryu, SJ, Lee, TH. Dehydration is an independent predictor of discharge outcome and admission cost in acute ischaemic stroke. *Eur J Neurol*. 2014;21:1184–91.
28. Lin LC, Lee JD, Hung YC, Chang CH, Yang JT. BUN/creatinine ratio based hydration for preventing stroke-in-evolution after acute ischemic stroke. *Am J Emerg Med*. 2014;32:709–712.

Figure Legend

Figure 1. Comparing 90-day functional outcome by modified Rankin Scale score for patients with and without VCS-20

Figure 2. Comparing 90-day functional outcome by modified Rankin Scale score for patients with and without VCS-30