MEDICAL COMPLICATIONS IN THE SURGICAL MANAGEMENT OF STROKE

by

Christian Daniel Cerecedo Lopez, MD

A Dissertation Submitted to the Faculty of Harvard Medical School

in Partial Fulfillment of

the Requirements for the Degree of Master of Medical Sciences in Clinical Investigation (MMSCI)

Harvard University

Boston, Massachusetts

March 2020

Area of Concentration: Neurology/Neurological Surgery.

External Reviewer: Aman B. Patel, MD

Content Advisor: Kai U. Frerichs, MD

Program Representative: Michael M. Mendelson, MD

Primary Mentor: Rose Du, MD, PhD

I have reviewed this thesis. It represents work done by the author under my guidance/supervision.

Primary Mentor: Rose Du, MD, PhD

Revised Apr 1, 2020

TABLE OF CONTENTS

ACKNOWLEDGMENTS

The author acknowledges the guidance of faculty members of the Master of Medical Science in Clinical Investigation program, the mentorship of Dr. Rose Du, the collaboration of other members of the Du Cerebrovascular Surgery Lab, and the financial support of his family and of Fundación México en Harvard A.C.

BACKGROUND

Stroke is an abrupt interruption of blood flow to the brain causing loss of neurological function. (1) In the United States, stroke is the leading cause of disability and the fifth most common cause of death. (2) Yearly stroke expenditures average $45.5 billion USD, making stroke one of the most expensive diseases in the country. (2) Stroke can be ischemic – when caused by thromboembolic obstruction – or hemorrhagic – when caused by a rupture in the cerebral vasculature. (1)

For decades, the management of ischemic stroke (IS) was primarily medical, with recombinant tissue plasma activator being the mainstay of treatment. Recently, the value of mechanical thrombectomy for IS management was proved by several randomized studies. (3–6) Mechanical thrombectomy is now recommended for patients with internal carotid artery or proximal middle cerebral artery occlusion in whom treatment can be initiated within 6 hours of stroke onset. (7) The adoption of endovascular interventions caused a shift in the settings in which IS patients are managed, with IS patients now being common in neurosurgical wards. (8) Understanding the medical complications of IS and their role in the perioperative management of IS patients is of paramount importance for optimizing the surgical care of stroke.

In contrast to IS, surgery has been the mainstay of treatment for aneurysmal subarachnoid hemorrhage (aSAH) – a subtype of hemorrhagic stroke. The experience accumulated by generations of cerebrovascular surgeons led to a decrease in surgical complications after aSAH.(9) Because surgical complications of aSAH are highly lethal, reductions in their incidence resulted in increased patient survival. (9) Outcomes of aSAH – however – remain suboptimal, with two-thirds of aSAH patients surviving aneurysm surgery facing death or disability.(9,10) Medical complications of aSAH may not be as lethal as surgical complications, but they are the main drivers of disability, making their study essential for aSAH outcome improvement.

Insulin in the Management of Acute Ischemic Stroke: A Systematic Review and Meta-Analysis

Christian D. Cerecedo-Lopez, MD[1], Alejandra Cantu-Aldana, MD[2], Nirav J. Patel, MD[1], M. Ali Aziz-Sultan, MD[1], Kai U. Frerichs, MD[1], Rose Du, MD, PhD[1,*]

[1] Department of Neurosurgery, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA

[2] Facultad de Ciencias de la Salud, Universidad Anáhuac México, Huixquilucan, Estado de México, México

***Corresponding author**

Rose Du, MD, PhD

Department of Neurosurgery

Brigham and Women's Hospital

75 Francis Street

Boston, MA 02115

Phone: 617-525-8132

Fax: 617-713-3050

Email: rdu@bwh.harvard.edu

Key words: hyperglycemia; stroke; glucose; insulin; meta-analysis

ABSTRACT

Objective: The role of tight glycemic control in the management of acute ischemic stroke remains uncertain. Our goal is to evaluate the effects of tight glucose control with insulin therapy after acute ischemic stroke.

Methods: We searched PubMed, CENTRAL, and EMBASE for randomized controlled trials (RCTs) that evaluated the effects of tight glycemic control (70 - 135 mg/dL) in acute ischemic stroke. Analysis was performed using fixed- and random-effects models. We evaluated the efficacy and safety of tight glycemic control, with our primary outcome of efficacy being independence at ≥90 days follow-up, and our primary outcome of safety being symptomatic or severe hypoglycemia during treatment. Secondary outcomes included death and independence.

Results: Twelve RCTs including 2,734 patients were included. When compared to conventional therapy or placebo, tight glycemic control was associated with similar mRS scores at ≥90 days follow-up (standardized mean difference, 0.014 [-0.15 – 0.17], I^2 0%), mortality at ≥90 days follow-up (pooled odds ratio [pOR], 0.99 [95% CI, 0.79 – 1.22], I^2 0%), and independence at ≥90 days follow-up (pOR, 0.95 [0.79 – 1.14], I^2 0%). In contrast, tight glycemic control was associated with increased rates of symptomatic or severe hypoglycemia during treatment (pOR 5.2 [1.7 – 15.9], I^2 28%).

Conclusions: Tight glucose control after acute ischemic stroke is not associated with improvements in mRS score, mortality or independence and leads to higher rates of symptomatic or severe hypoglycemia.

BACKGROUND

Hyperglycemia is common after acute ischemic stroke and is associated with poor outcomes including increased in-hospital mortality and poor neurological function.[1] Various mechanisms for the detrimental effects of hyperglycemia after acute ischemic stroke have been proposed, but a lack of consensus on the pathophysiology of hyperglycemia-aggravated secondary brain injury remains.[2] The concept of tight glycemic control as a potential strategy to ameliorate secondary brain injury associated with hyperglycemia emerged and led to various randomized controlled trials (RCTs) that evaluated tight glycemic control for the management of acute ischemic stroke and other critical illnesses. The use of tight glycemic control in the intensive care setting was recently evaluated in a systematic review and meta-analysis that showed no mortality benefit and a five-fold increase in hypoglycemic rates in critically ill patients under treatments aimed at tight glycemic control.[3] Similarly, a systematic review and meta-analysis performed by the Cochrane Collaboration in 2014 revealed no major clinical benefits from therapies aimed at tight glycemic control in patients with acute ischemic stroke.[4]

Novel evidence on the use of tight glycemic control for the management of acute ischemic stroke has become available. The results of the Stroke Hyperglycemia Insulin Network Effort (SHINE) trial were recently published.[5] The SHINE trial addressed many of the shortcomings of previously

published RCTs evaluating insulin for tight glycemic control after acute ischemic stroke, namely a high proportion of non-diabetic and hemorrhagic stroke individuals and lack of power.[6] With this in mind, we performed a systematic review and meta-analysis of previously published RCTs to evaluate the use of insulin for tight glycemic control in the management of patients with acute ischemic stroke. We restricted the scope of our review to studies reporting clinical outcomes.

METHODS

SYSTEMATIC REVIEW

This systematic review was performed following the guidelines of the Cochrane Handbook of Systematic Reviews and Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[7,8] The review protocol was submitted for registration in the International prospective register of systematic reviews (PROSPERO) and is currently pending final registration.

Medical Subject Headings (Embase Subject Headings for EMBASE) "stroke", "hyperglycemia" and "glucose" were fully exploded to search CENTRAL, PubMed and EMBASE for publications from inception to August 1, 2019, January 1, 2005 to August 1, 2019, and January 1, 2017 to August 1, 2019, respectively (Table 1 in Supplemental Digital Content). Studies were included that 1) were randomized controlled trials, 2) had subjects with acute ischemic stroke who had hyperglycemia on or shortly after admission, 3) had an intervention arm of tight glycemic control defined as insulin therapy aimed at maintaining blood glucose concentration between 70 – 135 mg/dL, 4) had a comparison arm of conventional subcutaneous insulin therapy and/or placebo, and

5) had at least one clinical outcome (e.g. survival, quality of life). No restrictions on length of follow-up were made. Two independent reviewers (CC and AC) screened the titles and abstracts using these prespecified study characteristics selecting citations for full-text review. The same independent reviewers performed a full-text review of the selected citations to determine the studies to be included. In cases of discordance, a consensus was reached after discussion.

To evaluate for the risk of bias, two independent reviewers (CC and AC) assessed the included papers using the revised version of the Cochrane risk-of-bias tool for randomized trials.[9] Each reviewer independently evaluated five domains of bias using the tool's CRIBSHEET as guidance. Scores were then compared, and discrepancies were solved through discussion.

META-ANALYSIS

Included studies were reviewed by both independent reviewers for extraction of the following information: first author, year, number of subjects randomized, demographics per group, length of follow-up, number of deceased subjects at the end of follow-up, number of independent subjects at the end of follow-up, mean and variance of validated stroke scale scores at the end of follow-up, and number of subjects who experienced at least one symptomatic or severe episode of hypoglycemia. The data obtained from both reviewers were then compared and any discrepancies were corrected by review of the study. Statistical analysis was performed using R version 3.5.3 (The R Foundation for Statistical Computing) and the *meta* package.[10,11] Data was analyzed with an intention-to-treat approach, using group sizes at the time of randomization for all analyses unless otherwise specified. Our efficacy and safety outcomes of primary interest were the independence at ≥90 days and symptomatic or severe hypoglycemia during insulin

treatment, respectively. Secondary outcomes included death and the modified Rankin Scale Score. Summary measures included pooled odds ratio and standardized mean difference for dichotomous (death, independence and symptomatic or severe hypoglycemia) and continuous (mean modified Rankin Scale (mRS) score) outcomes, respectively. Both fixed and random effects models were estimated.[8] Higgins I^2 statistic was used to measure heterogeneity.[12] Random effect models were used when $I^2 \geq 10$. Funnel plots were created to graphically assess small-study effects, and Begg and Mazumdar's Rank Correlation Test was used to test the null hypothesis of funnel plot symmetry.

RESULTS

STUDY CHARACTERISTICS

We obtained a total of 1,058 titles and abstracts from searching the databases, with 46 of these being duplicates, leaving 1,012 titles and abstracts for screening. Nine hundred and eighty-two abstracts and titles were excluded leaving 30 studies for full-text review. After full-text review, twelve studies with a total of 2,734 patients fulfilled the prespecified criteria and were included in this meta-analysis (Figure 1, Supplementary Table 2).[5,6,13–22] Average age was 70 years, half of the subjects were women (49%) and baseline characteristics between the intervention and control groups were balanced with 47% of enrolled subjects having previously diagnosed diabetes mellitus (Table 1). Length of follow-up ranged from 5 to 120 days (Table 1). Gray et al. 2007 (GIST-UK Trial) did not require CT imaging for diagnosis and thus included some subjects with intracerebral hemorrhage into their cohort.[6] These subjects were included in this meta-analysis. In all studies, the intervention in the experimental arm was intravenous insulin infusion. The control

interventions included standard therapy used at the research institution,[5,13–19] 0.9% saline solution as a placebo,[6,21] or a carbohydrate restrictive diet (Supplementary Table 2).[14] Functional outcomes were reported using the National Institutes of Health Stroke Scale,[13,16–19,21] Barthel Index,[13,15,17] European Stroke Scale,[6] Stroke Specific Quality-of-Life Scale,[13] modified Rankin Scale,[5,6,13,17,19,21] Extended Glasgow Comma Scale,[14] and Stroke Impact Scale (Supplementary Table 2).[17] Independence was defined as a favorable score in one of these scales. Severe or symptomatic hypoglycemia was defined as the presence of clinical and laboratory findings,[13,16–19,21] or laboratory findings only (i.e. less than a pre-specified serum glucose level, Supplementary Table 2).[5,20] Hypoglycemic events were not defined by Azevedo et al. 2009.[17]

RISK OF BIAS

All but four studies had an unclear risk of bias (Figure 2). The majority of the perceived bias arose from concerns in the measurement of the outcome (66%), as most of the studies included in this meta-analysis had an unblinded measurement of functional outcomes.[6,13–16,18,19,21] Other sources of perceived potential bias included a lack of analysis pre-specification,[13–15] unclear randomization procedures,[13,14] and a lack of information on potential deviations from the intended intervention.[14,16,21]

EFFICACY

Independence at ≥90 days of follow-up.

Analysis of 6 RCTs[5,6,13,16,19,22] including 2,424 subjects showed that tight glycemic control was not associated with higher odds of independence at ≥90 days of follow-up (FEM pOR, 0.95 [0.82 – 1.14], I^2 0% [0 – 18.9%]) (Figure 3; Supplementary Figure 1). No strong graphical or statistical

evidence suggestive of publication bias for this outcome was found (rank correlation test p-value 0.09) (Supplementary Figure 2).

Mortality at ≥90 days of follow-up.

Analysis of 6 RCTs[5,6,13,16,19,22] including 2,424 subjects showed that tight glycemic control was not associated with lower odds of mortality at ≥90 days of follow-up (fixed effects model [FEM] pooled odds ratio [pOR], 0.99 [0.79 – 1.22], I^2 0% [0 – 71.3%]) (Figure 3; Supplementary Figure 1). No graphical or statistical evidence suggestive of publication bias for this outcome was found (rank correlation test p-value 0.82) (Supplementary Figure 2).

Modified Rankin Scale score at ≥90 days of follow-up.

Analysis of 3 RCTs[5,6,22] including 2,124 subjects showed that tight glycemic control was not associated with differences in mRS scores at ≥90 days of follow-up (FEM standardized mean difference [SMD], 0.01 [-0.15 – 0.17], I^2 0% [0 – 77.7%]) (Figure 3, Supplementary Figure 1). No graphical or statistical evidence suggestive of publication bias for this outcome was found (rank correlation test p-value 0.93) (Supplementary Figure 2).

SAFETY

Symptomatic or severe hypoglycemia during treatment.

Analysis of 11 RCTs[5,6,13–22] including 2,612 subjects showed that tight glycemic control was associated with higher rates of symptomatic or severe hypoglycemia during treatment (random effects model pOR, 5.2 [1.7 – 15.9], I^2 28% [0 – 67.5%]) (Figure 3, Supplementary Figure 1). No

strong graphical or statistical evidence suggestive of publication bias for this outcome was found (rank correlation test p-value 0.06) (Supplementary Figure 2).

DISCUSSION

Compared with conventional therapy, insulin therapy aimed at tight glycemic control after acute ischemic stroke is associated with similar mortality and independence rates, non-superior mRS scores, and an approximately five-fold increase in the odds of symptomatic or severe hypoglycemia. These findings are consistent with those of a previous systematic review and meta-analysis evaluating the use of insulin for tight glycemic control in critically ill patients managed in the intensive care setting.[3]

Although similar results were observed in a systematic review and meta-analysis evaluating the use of tight glycemic control in the management of acute ischemic stroke in 2014,[4] current stroke guidelines acknowledge evidence supporting conventional insulin therapy after acute ischemic stroke is limited, mainly due to shortcomings of previously published RCTs.[23] By incorporating the findings of the SHINE trial, we expect our meta-analysis to provide further confidence to future recommendations on the management of hyperglycemia after acute ischemic stroke.

Interest in the role of hyperglycemia as a mediator of secondary brain injury remains. Mechanical thrombectomy is now considered standard treatment for delayed-onset acute ischemic stroke.[24] Understanding the mechanisms behind hyperglycemia mediated secondary brain injury in mechanical thrombectomy patients is perhaps even more pressing as hyperglycemia appears to

have unique effects in this setting.[25] Because mechanical thrombectomy was approved as standard therapy for ischemic stroke in recent years, only a small proportion of patients in one of the papers included in this meta-analysis underwent mechanical thrombectomy.[26] Further studies evaluating glucose management strategies in this subset of the stroke patient population may provide further insights into this matter.

Approved and experimental medications targeting hyperglycemia continue to be studied as potential therapies for secondary brain injury including metformin and sitagliptin,[27] sulfonylureas,[28,29] epoxide hydrolase inhibitors,[30] glucose transporter inhibitors,[31] valproic acid,[32] and glucagon-like peptide agonists.[33–35] A member of this latter group of compounds is being evaluated in the Short-Term EXenatide therapy in Acute ischaemic Stroke (STEXAS) trial.[36] Alternatively, pathways associated with insulin have been proposed as potential therapeutic targets for secondary brain injury associated with hyperglycemia.[37,38] The findings of this meta-analysis are, therefore, timely and sobering. Insulin may be the gold standard for the management of hyperglycemia in other conditions but appears to be ineffective in improving outcomes in patients with acute ischemic stroke. Novel therapeutic approaches for the management of hyperglycemia-mediated secondary brain injury are needed.

LIMITATIONS

Most studies included in this review had an unblinded outcome assessment.[14–18,20–22] This may be particularly worrisome when evaluating outcomes that are highly dependent on the observer's interpretation (e.g. mRS).[39] Additionally, most studies were exploratory in nature and were therefore underpowered.[13,17–20,22] Only two of the included studies were designed to assess efficacy

signals in the data: the GIST-UK trial and the SHINE trial.[5,6] Due to their larger sample sizes in comparison to other studies, the GIST-UK and SHINE trials provided the largest contribution to the efficacy analyses (80 – 90%).[5,6] Because both of these large studies were performed in the same center, the efficacy of insulin therapy in different settings may be different.[5,6] The strong safety signal indicating that tight glycemic control is associated with symptomatic or severe hypoglycemia, however, was assessed by all of the included studies and should be strongly considered if additional trials evaluating tight glycemic control in other settings are planned. Finally, length of follow-up was short for half of the included studies limiting the number of studies in which outcomes at ≥90 days were analyzed.[14,15,17,18,20,21]

CONCLUSION

In this meta-analysis of RCTs of patients with acute ischemic stroke, evidence showed that, when compared to standard glucose management strategies, insulin therapy aimed at strict glucose control is not associated with improvements in mortality, independence, or modified Rankin Scale scores and is associated with higher rates of symptomatic or severe hypoglycemia.

REFERENCES

1. Capes SE, Hunt D, Malmberg K, Pathak P, Gerstein HC. Stress Hyperglycemia and Prognosis of Stroke in Nondiabetic and Diabetic Patients A Systematic Overview. *Stroke*. 2001;32:2426-2432.

2. Kruyt ND, Biessels GJ, Devries JH, Roos YB. Hyperglycemia in acute ischemic stroke:

pathophysiology and clinical management. *Nat Rev Neurol*. 2010;6(3):145-155. doi:10.1038/nrneurol.2009.231

3. Yamada T, Shojima N, Noma H, Yamauchi T, Kadowaki T. Glycemic control , mortality , and hypoglycemia in critically ill patients : a systematic review and network meta - analysis of randomized controlled trials. *Intensive Care Med*. 2017;43(1):1-15. doi:10.1007/s00134-016-4523-0

4. Bellolio MF, Gilmore RM, Stead LG. Insulin for glycaemic control in acute ischaemic stroke. *Cochrane database Syst Rev*. 2011;(9):CD005346. doi:10.1002/14651858.CD005346.pub3

5. Johnston KC, Bruno A, Pauls Q, et al. Intensive vs Standard Treatment of Hyperglycemia and Functional Outcome in Patients With Acute Ischemic Stroke The SHINE Randomized Clinical Trial. *JAMA*. 2019;322(4):326-335. doi:10.1001/jama.2019.9346

6. Gray CS, Hildreth AJ, Sandercock PA, et al. Glucose-potassium-insulin infusions in the management of post-stroke hyperglycaemia: the UK Glucose Insulin in Stroke Trial (GIST-UK). *Lancet Neurol*. 2007;6(5):397-406. doi:10.1016/S1474-4422(07)70080-7

7. Moher D, Liberati A, Tetzlaff J, Altman DG, Group TP. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLOS Med*. 2009;6(7):e1000097. https://doi.org/10.1371/journal.pmed.1000097.

8. Higgins J, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [Updated March 2011]*.; 2011.

9. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928. doi:10.1136/bmj.d5928

10. Team RC, R Core Team. R: A language and environment for statistical computing. 2018.

https://www.r-project.org/.

11. Schwarzer G. meta: An R package for meta-analysis. *R News*. 2007:40-45. https://cran.r-project.org/doc/Rnews/Rnews_2007-3.pdf.

12. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-560. doi:10.1136/bmj.327.7414.557

13. Bruno A, Kent TA, Coull BM, et al. Treatment of Hyperglycemia In Ischemic Stroke (THIS) A Randomized Pilot Trial. *Stroke*. 2008;39(2):384-389. doi:10.1161/STROKEAHA.107.493544

14. Staszewski J, Brodacki B, Kotowicz J, Stepien A. Intravenous insulin therapy in the maintenance of strict glycemic control in nondiabetic acute stroke patients with mild hyperglycemia. *J Stroke Cerebrovasc Dis*. 2011;20(2):150-154. doi:10.1016/j.jstrokecerebrovasdis.2009.11.013

15. Vinychuk SM, Melnyk S, Margitich VM. Hyperglycemia after Acute Ischemic Stroke : Prediction, Significance and Immediate Control with Insulin-Potassium-Saline-Magnesium. *Hear Drug*. 2005;5:197-204. doi:10.1159/000089600

16. Rosso C, Corvol J-C, Pires C, et al. Intensive Versus Subcutaneous Insulin in Patients With Hyperacute Stroke. *Stroke*. 2012;43(9):2343-2349. doi:10.1161/strokeaha.112.657122

17. Azevedo J, Azevedo R, Miranda M, Costa N, Araujo L. Management of hyperglycemia in patients with acute ischemic stroke. *Crit Care*. 2009;13(Suppl 3):48. doi:10.1186/cc7850

18. Walters MR, Weir CJ, Lees KR. A randomised, controlled pilot study to investigate the potential benefit of intervention with insulin in hyperglycaemic acute ischaemic stroke patients. *Cerebrovasc Dis*. 2006;22(2-3):116-122. doi:10.1159/000093239

19. Johnston KC, Hall CE, Kissela BM, Bleck TP, Conaway MR. Glucose Regulation in

Acute Stroke Patients (GRASP) Trial. *Stroke*. 2009;40(12):3804-3809. doi:10.1161/strokeaha.109.561498

20. Vriesendorp TM, Roos YB, Kruyt ND, et al. Efficacy and safety of two 5 day insulin dosing regimens to achieve strict glycaemic control in patients with acute ischaemic stroke. *J Neurol Neurosurg Psychiatry*. 2009;80(9):1040-1043. doi:10.1136/jnnp.2008.144873

21. McCormick M, Hadley D, McLean JR, Macfarlane JA, Condon B, Muir KW. Randomized, controlled trial of insulin for acute poststroke hyperglycemia. *Ann Neurol*. 2010;67(5):570-578. doi:10.1002/ana.21983

22. Kreisel SH, Berschin UM, Hammes H-PP, et al. Pragmatic management of hyperglycaemia in acute ischaemic stroke: Safety and feasibility of intensive intravenous insulin treatment. *Cerebrovasc Dis*. 2009;27(2):167-175. doi:10.1159/000185608

23. Powers WJ, Rabinstein AA, Ackerson T, 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*. Vol 49.; 2018. doi:10.1161/STR.0000000000000158

24. Jansen IGH, Mulder MJHL, Goldhoorn RJB. Endovascular treatment for acute ischaemic stroke in routine clinical practice: Prospective, observational cohort study (MR CLEAN Registry). *BMJ*. 2018;360. doi:10.1136/bmj.k949

25. Osei E, den Hertog HM, Berkhemer OA, et al. Increased admission and fasting glucose are associated with unfavorable short-term outcome after intra-arterial treatment of ischemic stroke in the MR CLEAN pretrial cohort. *J Neurol Sci*. 2016;371:1-5. doi:10.1016/j.jns.2016.10.003

26. Bruno A, Durkalski VL, Hall CE, et al. The Stroke Hyperglycemia Insulin Network

Effort (SHINE) trial protocol: A randomized, blinded, efficacy trial of standard vs. intensive hyperglycemia management in acute stroke. *Int J Stroke*. 2014;9(2):246-251. doi:10.1111/ijs.12045

27. Osei E, Fonville S, Zandbergen AAM, et al. Metformin and sitAgliptin in patients with impAired glucose tolerance and a recent TIA or minor ischemic Stroke (MAAS): study protocol for a randomized controlled trial. *Trials*. 2015;16:332. doi:10.1186/s13063-015-0882-z

28. Simard JM, Yurovsky V, Tsymbalyuk N, Melnichenko L, Ivanova S, Gerzanich V. Protective effect of delayed treatment with low-dose glibenclamide in three models of ischemic stroke. *Stroke*. 2009;40(2):604-609. doi:10.1161/STROKEAHA.108.522409

29. Tan F, Li H, Ma M, Yu Y. Protective effect of treatment with low-dose gliclazide in a model of middle cerebral artery occlusion and reperfusion in rats. *Brain Res*. 2014;1560:83-90. doi:10.1016/j.brainres.2014.02.044

30. Jouihan SA, Zuloaga KL, Zhang W, et al. Role of soluble epoxide hydrolase in exacerbation of stroke by streptozotocin-induced type 1 diabetes mellitus. *J Cereb Blood Flow Metab*. 2013;33(10):1650-1656. doi:10.1038/jcbfm.2013.130

31. Zhang S, Zuo W, Guo X-F, He W-B, Chen N-H. Cerebral glucose transporter: the possible therapeutic target for ischemic stroke. *Neurochem Int*. 2014;70:22-29. doi:10.1016/j.neuint.2014.03.007

32. Suda S, Ueda M, Nito C, et al. Valproic acid ameliorates ischemic brain injury in hyperglycemic rats with permanent middle cerebral occlusion. *Brain Res*. 2015;1606:1-8. doi:10.1016/j.brainres.2015.02.013

33. Sato K, Kameda M, Yasuhara T, et al. Neuroprotective effects of liraglutide for stroke model of rats. *Int J Mol Sci*. 2013;14(11):21513-21524. doi:10.3390/ijms141121513

34. Zhang H, Liu Y, Guan S, et al. An Orally Active Allosteric GLP-1 Receptor Agonist Is Neuroprotective in Cellular and Rodent Models of Stroke. *PLoS One*. 2016;11(2):e0148827. doi:10.1371/journal.pone.0148827

35. Kuroki T, Tanaka R, Shimada Y, et al. Exendin-4 Inhibits Matrix Metalloproteinase-9 Activation and Reduces Infarct Growth After Focal Cerebral Ischemia in Hyperglycemic Mice. *Stroke*. 2016;47(5):1328-1335. doi:10.1161/STROKEAHA.116.012934

36. McGrath RT, Hocking SL, Priglinger M, et al. Rationale and design of Short-Term EXenatide therapy in Acute ischaemic Stroke (STEXAS): a randomised, open-label, parallel-group study. *BMJ Open*. 2016;6(2):e008203. doi:10.1136/bmjopen-2015-008203

37. Cerecedo-Lopez CD, Kim-Lee JH, Hernandez D, Acosta SA, Borlongan C V. Insulin-associated neuroinflammatory pathways as therapeutic targets for traumatic brain injury. *Med Hypotheses*. 2014;82(2):171-174. doi:10.1016/j.mehy.2013.11.028

38. Khan MA, Schultz S, Othman A, et al. Hyperglycemia in Stroke Impairs Polarization of Monocytes/Macrophages to a Protective Noninflammatory Cell Type. *J Neurosci*. 2016;36(36):9313-9325. doi:10.1523/JNEUROSCI.0473-16.2016

39. Quinn TJ, Dawson J, Walters MR, Lees KR. Exploring the Reliability of the Modified Rankin Scale. 2009:762-766. doi:10.1161/STROKEAHA.108.522516

TABLES AND FIGURES

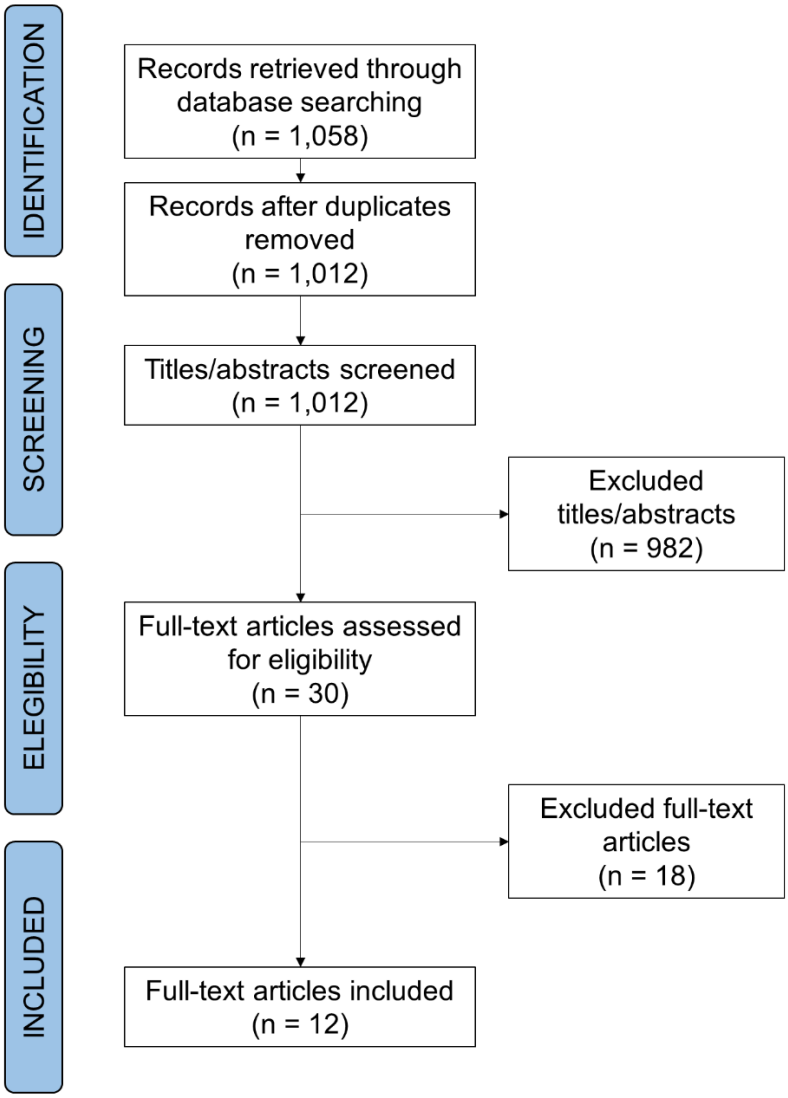


Figure 1. PRISMA flow chart for systematic review.

Figure 2. Cochrane risk of bias assessment tool for randomized studies. + (green): low risk of bias, ? (yellow): some concerns for bias, – (red): high risk of bias.

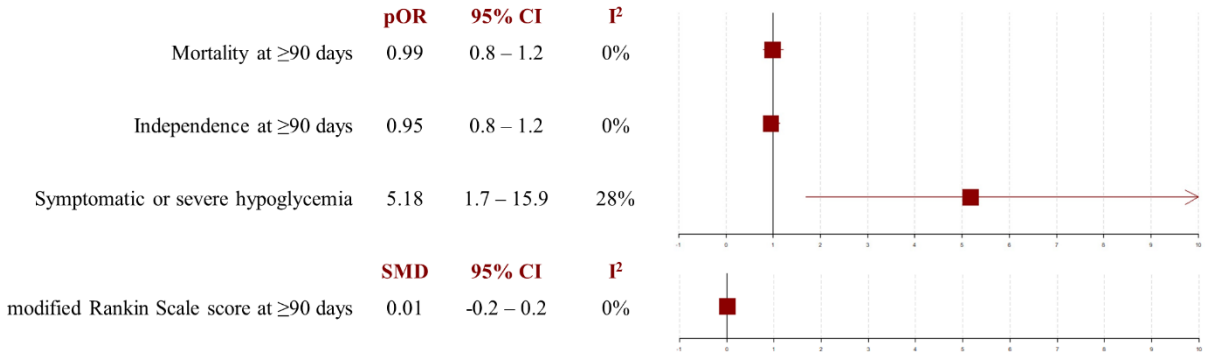


Figure 3. Summary of main results for meta-analysis. Box denotes point estimate, horizontal lines denote confidence intervals, solid vertical lines denote value of null hypothesis for a given analysis.

Table 1. Summary of outcomes from included studies.

Study	**Arm**	**Subjects** n (%)	**Age** yrs (±SD)	**Female** n (%)	**Diabetes** n (%)	**Follow-up** days	**Mortality at latest follow-up** n (%)	**Independence at latest follow-up** n (%)	**Disability at latest follow-up**[γ] n (%)	**Symptomatic or severe hypoglycemia** n (%)
Vinychuk et al. 2005[12]	intervention	61 (48)	62.6 ±1.3	33 (54)	36 (59)	30	*NA*	13 (21)	8.72 ±1.2	*NA*
	control	67 (52)	62.4 ±1.3	37 (55)	40 (60)	30	*NA*	11 (16)	9.38 ±1.3	*NA*
Walters et al. 2006[17]	intervention	13 (52)	73.3 ±12.5	8 (62)	7 (54)	30	1 (8)	*NA*	4 ±4.3	1 (8)
	control	12 (48)	76.7 ±9.5	7 (58)	6 (50)	30	0 (0)	*NA*	6.5 ±2.8	0 (0)
Gray et al. 2007[22]	intervention	464 (50)	75.7 ±9.4	250 (54)	79 (17)	90	139 (30)	124 (27)	73.4 ±24.6	73 (16)
	control	469 (50)	74.8 ±10.3	262 (56)	75 (16)	90	128 (27)	136 (29)	74.5 ±23.8	0 (0)
Bruno et al. 2008[13]	intervention	31 (67)	62 ±15	14 (45)	31 (100)	90	2 (6)	16 (52)	3.57 ±1.1	5 (16)
	control	15 (33)	53 ±15	6 (40)	11 (73)	90	0 (0)	7 (47)	3.63 ±1	0 (0)
Johnston et al. 2009[18]	intervention	24 (32)	68 ±4	11 (46)	12 (50)	90	3 (13)	10 (42)	68.7 ±19.1	0 (0)
	control	50 (68)	68.5 ±5.3	22 (44)	32 (64)	90	7 (14)	15 (30)	69 ±23	1 (2)
Kreisel et al. 2009[21]	intervention	20 (50)	72.3 ±9.5	5 (25)	6 (30)	120	5 (25)	5 (25)	2 ±1.3	3 (15)
	control	20 (50)	71 ±10.8	11 (55)	7 (35)	120	3 (15)	5 (25)	2 ±1.3	0 (0)
Azevedo et al. 2009[16]	intervention	14 (41)	*NA*	*NA*	*NA*	*NA*[β]	4 (29)	1 (7)	*NA*	1 (7)
	control	20 (59)	*NA*	*NA*	*NA*	*NA*[β]	6 (30)	5 (25)	*NA*	2 (10)
Vriesendorp et al. 2009[19]	intervention	23 (47)[α]	75.2 ±11.7	11 (48)	8 (35)	5	*NA*	*NA*	2 ±5.3	1 (4)
	control	16 (33)[α]	64.7 ±17.5	8 (50)	0 (0)	5	*NA*	*NA*	2 ±4.8	0 (0)
McCormick et al. 2010[20]	intervention	25 (63)	75.1 ±11	14 (56)	7 (28)	30	2 (8)	4 (16)	4 ±7	1 (4)
	control	15 (37)	74.7 ±7.1	10 (66)	6 (40)	30	0 (0)	2 (13)	8 ±9.9	0 (0)
Staszewski et al. 2011[14]	intervention	26 (52)	68 ±10	10 (40)	0 (0)	30	1 (4)	12 (46)	4 ±3	2 (8)
	control	24 (48)	87 ±9	13 (55)	0 (0)	30	2 (8)	7 (29)	7 ±4	0 (0)
Rosso et al. 2012[15]	intervention	90 (50)	69.6 ±*NA*	43 (43)[δ]	7 (8)[δ]	90[ε]	9 (10)	41 (46)	11 ±8.9	0 (0)
	control	90 (50)	76.9 ±*NA*	37 (48)[δ]	15 (17)[δ]	90[ε]	14 (16)	41 (46)	10.5 ±11.1	0 (0)

Johnston et al. 2019[5]	intervention	581 (50)	66 ±13.3	260 (49)	468 (81)	90	54 (9)	119 (21)	2.5 ±1.9	15 (3)
	control	570 (50)	66 ±14	264 (46)	455 (80)	90	65 (11)	123 (22)	2.6 ±1.8	0 (0)

NA=information not available or not estimable. α: percentages do not add to 100 because an additional group was not included in this review. β: subjects were followed until hospital discharge. γ: different stroke scales were used to report disability scores. δ: percentages estimated from per-protocol population. ε: length of follow-up differed between outcomes.

SUPPLEMENTARY MATERIAL
Insulin in the Management of Acute Ischemic Stroke: A Systematic Review and Meta-Analysis.

Supplementary Table 1. Search statements and limits.

Database	Statement	Limits	Other filters	Expanded Search Statement
CENTRAL	#1 MeSH descriptor: [Stroke] explode all trees #2 MeSH descriptor: [Glucose] explode all trees #3 #1 AND #2	None	Trials	(Infarction, Middle Cerebral Artery OR Right Middle Cerebral Artery Infarction OR Middle Cerebral Artery Thrombotic Infarction OR Thrombotic Infarction, Middle Cerebral Artery OR Middle Cerebral Artery Circulation Infarction OR Left Middle Cerebral Artery Infarction OR Middle Cerebral Artery Embolic Infarction OR Embolic Infarction, Middle Cerebral Artery OR Thrombosis, Middle Cerebral Artery OR Middle Cerebral Artery Thrombosis OR Middle Cerebral Artery Syndrome OR Stroke, Middle Cerebral Artery OR Middle Cerebral Artery Infarction OR Middle Cerebral Artery Stroke OR Cerebral Infarction, Middle Cerebral Artery OR Embolus, Middle Cerebral Artery OR Middle Cerebral Artery Embolus OR Occlusion, Middle Cerebral Artery OR Middle Cerebral Artery Occlusion OR MCA Infarction) OR (Infarction, Anterior Cerebral Artery OR Infarction, Anterior Cerebral Artery Distribution OR Infarction, Anterior Cerebral Artery Circulation OR Syndrome, Anterior Cerebral Artery OR Anterior Cerebral Artery Syndrome OR Anterior Cerebral Artery Stroke OR Anterior Cerebral Artery Infarction OR Stroke, Anterior Cerebral Artery OR Infarction, Heubner Artery OR Heubner Artery Infarction OR Artery Infarction, Heubner OR Artery Infarction, Heubner's OR Heubners Artery Infarction OR Infarction, Heubner's Artery OR Heubner's Artery Infarction OR Infarctions, ACA OR Infarction, ACA OR ACA Infarction OR ACA Infarctions) OR (Stroke Volume OR End-Diastolic Volume, Ventricular OR Volume, Ventricular End-Diastolic OR End-Diastolic Volumes, Ventricular OR Ventricular End-Diastolic Volume OR Volumes, Ventricular End-Diastolic OR Ventricular End Diastolic Volume OR Ventricular End-Diastolic Volumes OR Ventricular End Systolic Volume OR End-Systolic Volume, Ventricular OR End-Systolic Volumes, Ventricular OR Volume, Ventricular End-Systolic OR Volumes, Ventricular End-Systolic OR Ventricular End-Systolic Volume OR Ventricular End-Systolic Volumes OR Ventricular Ejection Fractions OR Fractions, Ventricular Ejection OR Fraction, Ventricular Ejection OR Ejection Fraction, Ventricular OR Ventricular Ejection Fraction OR Ejection

				Fractions, Ventricular OR Stroke Volumes; Volume, Stroke OR Volumes, Stroke) OR (Brain Stem Infarction OR Top of the Basilar Syndrome OR Infarctions, Brain Stem OR Brain Stem Infarction OR Infarction, Brain Stem OR Millard-Gublar Syndrome OR Millard Gublar Syndrome OR Syndrome, Millard-Gublar OR Infarctions, Brainstem OR Brainstem Infarctions OR Stroke, Brainstem OR Infarction, Brainstem OR Brainstem Infarction OR Brainstem Stroke OR Claude Syndrome OR Foville Syndrome OR Weber Syndrome OR Benedict Syndrome) OR (Infarction, Posterior Cerebral Artery OR Posterior Cerebral Artery Embolic Infarction OR Embolic Infarction, Posterior Cerebral Artery OR Posterior Cerebral Artery Thrombotic Infarction OR Thrombotic Infarction, Posterior Cerebral Artery OR Posterior Cerebral Artery Infarction OR Posterior Cerebral Artery Stroke OR Stroke, Posterior Cerebral Artery OR Posterior Cerebral Artery Syndrome OR PCA Infarction OR Infarction, PCA) OR (MELAS Syndrome OR Mitochondrial Myopathy, Encephalopathy, Lactic Acidosis, And Stroke-Like Episodes OR Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-Like Episodes OR Mitochondrial Myopathy, Lactic Acidosis, Stroke-Like Episode OR Myopathy, Mitochondrial-Encephalopathy-Lactic Acidosis-Stroke OR Syndrome, MELAS OR MELAS) OR (National Institute of Neurological Disorders and Stroke (U.S.) OR National Institute of Neurological Disorders and Stroke (U.S.) OR National Institute of Neurological Disorders and Stroke OR NINDS) OR (Cardiovascular Strokes OR Infarct, Myocardial OR Myocardial Infarct OR Infarcts, Myocardial OR Myocardial Infarcts OR Infarction, Myocardial OR Myocardial Infarctions OR Heart Attacks OR Cardiovascular Stroke OR Strokes, Cardiovascular OR Stroke, Cardiovascular OR Heart Attack OR Infarctions, Myocardial) OR (Lacunar Syndrome OR Lacunar Syndromes OR Syndrome, Lacunar OR Strokes, Lacunar OR Syndromes, Lacunar OR Lacunar Strokes OR Lacunar Stroke OR Lacunar Infarct OR Infarctions, Lacunar OR Infarction, Lacunar OR Infarct, Lacunar OR Lacunar Infarcts OR Infarcts, Lacunar OR Lacunar Infarctions OR Lacunar Infarction) OR (Acute Cerebrovascular Accidents OR Cerebrovascular Accident, Acute OR Cerebrovascular Accidents, Acute OR Acute Cerebrovascular Accident OR Brain Vascular Accidents OR CVA OR Vascular Accidents, Brain OR Brain Vascular Accident OR CVAs OR Vascular Accident, Brain OR Acute Stroke OR Acute Strokes OR Stroke, Acute OR Strokes, Acute OR Cerebrovascular Stroke OR Strokes, Cerebrovascular OR Cerebrovascular Apoplexy OR Cerebrovascular Accident OR Cerebrovascular Accidents OR Cerebral Stroke OR Cerebrovascular Strokes OR Cerebral Strokes OR Stroke, Cerebral OR Stroke, Cerebrovascular OR Strokes, Cerebral OR Apoplexy, Cerebrovascular OR Strokes OR Apoplexy) OR (Lightning Injuries OR Lightning Strokes OR Strokes, Lightning OR Stroke, Lightning OR Lightning Stroke OR Lightning Injury OR Injuries, Lightning OR Injury, Lightning) OR (Sunstroke OR Sun Strokes OR Sun Stroke OR Sunstrokes) OR (Heat Stroke OR Heat Strokes OR Stroke, Heat OR Strokes, Heat OR Heatstroke OR Heatstrokes) OR (Stroke Rehabilitation OR Rehabilitation, Stroke) AND (Glutamine-Fructose-6-Phosphate Transaminase OR 2-Amino-2-Deoxy-D-Glucose-6-Phosphate Ketol-Isomerase OR 2 Amino 2 Deoxy D Glucose 6 Phosphate Ketol Isomerase OR Ketol-Isomerase, 2-Amino-2-Deoxy-D-Glucose-6-Phosphate OR Glutamine-Fructose-6-Phosphate Transaminase OR Glutamine Fructose 6 P Aminotransferase OR Glutamine-Fructose-6-P Aminotransferase OR Glutamine-Fructose-6-Phosphate Aminotransferase OR Aminotransferase, Glutamine-Fructose-6-P OR Glutamine Fructose 6 Phosphate Aminotransferase OR Aminotransferase, Glutamine-Fructose-6-Phosphate OR Glucosaminephosphate Isomerase OR Glucosamine 6 Phosphate Synthetase OR Glucosamine-6-Phosphate Synthase OR Glutamine:Fructose-6-Phosphate-Amidotransferase OR Glucosamine 6 Phosphate Synthase OR Glucosaminephosphate Isomerase OR Glucosamine 6-Phosphate Synthetase OR 6-Phosphate Synthetase, Glucosamine OR Glutamine:Fructose 6

				Phosphate Amidotransferase OR Aminotransferase, Hexosephosphate OR Hexosephosphate Aminotransferase OR Glucosamine Synthetase) OR Starch Synthase OR ADP Glucose Starch Glucosyltransferase OR Granule Bound Starch Synthase OR Synthase, Granule-Bound Starch OR Granule-Bound Starch Synthase OR Starch (Bacterial Glycogen) Synthase OR Starch Synthase, Granule-Bound OR Synthase, Starch OR GBSS OR Fluorodeoxyglucose F18 OR 2 Fluoro 2 deoxy D glucose OR 2-Fluoro-2-deoxy-D-glucose OR 2-Fluoro-2-deoxyglucose OR 2 Fluoro 2 deoxyglucose OR Fluorodeoxyglucose F 18 OR Fludeoxyglucose F 18 OR F 18, Fluorodeoxyglucose OR Fluorine-18-fluorodeoxyglucose OR Fluorine 18 fluorodeoxyglucose OR F 18, Fludeoxyglucose OR 18F Fluorodeoxyglucose OR Fluorodeoxyglucose, 18F OR 18F-FDG OR F18, Fluorodeoxyglucose OR 18FDG OR Glucose Transporter Type 5 OR GLUT 5 Protein OR GLUT-5 Protein OR D-Fructose Transporter OR GLUT5 Protein OR SLC2A5 Protein OR Monosaccharide Transport Proteins OR Erythrocyte Band 4.5 Protein OR Transport-Inducing Protein, Glucose OR Glucose Transport Inducing Protein OR Glucose Transport-Inducing Protein OR 4.5 Preactin, Band OR Band 4.5 Preactin OR Preactin, Band 4.5 OR Proteins, Monosaccharide Transport OR Transport Proteins, Monosaccharide OR Transport Proteins, Hexose OR Hexose Transport Proteins OR Hexose Transporter OR Glycogen Storage Disease Type I OR Glycogen Storage Disease 1 (GSD I) OR Deficiency, Glucose-6-Phosphatase OR Glucose-6-Phosphatase Deficiency OR Deficiencies, Glucose-6-Phosphatase OR Glucose-6-Phosphatase Deficiencies OR Glucose 6 Phosphatase Deficiency OR Hepatorenal Glycogen Storage Disease OR Disease, von Gierke's OR von Gierke Disease OR Disease, von Gierke OR von Gierke's Disease OR von Gierkes Disease OR Gierkes Disease OR Disease, Gierke's OR Glycogenosis 1 OR Gierke's Disease OR Deficiencies, Glucosephosphatase OR Deficiency, Glucosephosphatase OR Gierke Disease OR Glucosephosphatase Deficiencies OR Glucosephosphatase Deficiency OR Disease, Gierke OR Glycogen Synthase OR UDP Glucose Glycogen Glucosyl Transferase OR UDP-Glucose Glycogen Glucosyl Transferase OR Glycogen Synthase I OR Glycogen (Starch) Synthase OR Synthase D OR Glycogen Synthetase OR Synthase, Glycogen OR Synthetase, Glycogen OR Synthase I OR Acetylglucosamine OR 2 Acetamido 2 Deoxy D Glucose OR 2-Acetamido-2-Deoxy-D-Glucose OR N-Acetyl-D-Glucosamine OR N Acetyl D Glucosamine OR 2-Acetamido-2-Deoxyglucose OR 2 Acetamido 2 Deoxyglucose OR Glucose Transporter Type 3 OR Solute Carrier Family 2, Facilitated Glucose Transporter, Member 3 Protein OR GLUT 3 Protein OR GLUT-3 Protein OR GLUT3 Protein OR SLC2A3 Protein OR Glucose Transporter Type 2 OR Solute Carrier Family 2, Facilitated Glucose Transporter, Member 2 Protein OR GLUT-2 Protein OR GLUT 2 Protein OR SLC2A2 Protein OR GLUT2 Protein OR Streptozocin OR 2-Deoxy-2-((methylnitrosoamino)carbonyl)amino-D-glucose OR Streptozotocine OR Streptozotocin OR Zanosar OR Glucosephosphate Dehydrogenase Deficiency OR Deficiency of Glucose 6 Phosphate Dehydrogenase OR Hemolytic Anemia Due to G6PD Deficiency OR Deficiency of Glucose-6-Phosphate Dehydrogenase OR Dehydrogenase Deficiencies, Glucose-6-Phosphate OR Glucose 6 Phosphate Dehydrogenase Deficiency OR Deficiency, Glucose-6-Phosphate Dehydrogenase OR Glucose-6-Phosphate Dehydrogenase Deficiencies OR Deficiencies, Glucose-6-Phosphate Dehydrogenase OR Dehydrogenase Deficiency, Glucose-6-Phosphate OR Glucose-6-Phosphate Dehydrogenase Deficiency OR Glucosephosphate Dehydrogenase Deficiencies OR Deficiency, Glucosephosphate Dehydrogenase OR Dehydrogenase Deficiency, Glucosephosphate OR Deficiencies, Glucosephosphate

				Dehydrogenase OR Dehydrogenase Deficiencies, Glucosephosphate OR Deficiency, GPD OR G6PD Deficiency OR Deficiencies, GPD OR Deficiencies, G6PD OR Deficiency, G6PD OR G6PD Deficiencies OR GPD Deficiency OR GPD Deficiencies OR Glucose-6-Phosphate Isomerase OR Tumor Cell Autocrine Motility Factor OR Tumor-Cell Autocrine Motility Factor OR Tumor Autocrine Motility Factor OR Isomerase, Glucose 6 Phosphate OR Glucose 6 Phosphate Isomerase OR Isomerase, Glucose-6-Phosphate OR Motility Factor, Autocrine OR Autocrine Motility Factor OR Phosphohexose Isomerase OR Phosphoglucose Isomerase OR Glucosephosphate Isomerase OR Isomerase, Phosphoglucose OR Isomerase, Glucosephosphate OR Isomerase, Phosphohexose OR Neuroleukin OR High Fructose Corn Syrup OR High Fructose Maize Syrup OR High-Fructose Maize Syrup OR Syrup, High-Fructose Maize OR Maize Syrup, High-Fructose OR Glucose-Fructose Syrup OR Glucose Fructose Syrup OR Syrup, Glucose-Fructose OR Corn Sugar OR Syrup, Maize OR Maize Syrup OR Sugar, Corn OR Isoglucose OR UDPglucose 4-Epimerase AND 4-Epimerase, UDP-Glucose OR UDP Glucose 4 Epimerase OR UDP-Glucose 4-Epimerase OR UDP-Galactose 4-Epimerase OR UDP Galactose 4 Epimerase OR 4-Epimerase, UDP-Galactose OR Uridine Diphosphate Glucose Epimerase OR UDPgalactose 4 Epimerase OR Epimerase, UDP Glucose OR 4-Epimerase, UDPgalactose OR UDPglucose 4 Epimerase OR Galactose Epimerase, UDP OR UDP Glucose Epimerase OR 4-Epimerase, UDPglucose OR Glucose Epimerase, UDP OR UDPgalactose 4-Epimerase OR Epimerase, UDP Galactose OR UDP Galactose Epimerase OR 3-O-Methylglucose OR 3-O-Methyl-D-Glucose OR 3 O Methyl D Glucose OR 3 O Methylglucose OR Sodium-Glucose Transporter 2 Inhibitors OR Sodium Glucose Transporter 2 Inhibitors OR SGLT-2 Inhibitors OR SGLT 2 Inhibitors OR SGLT2 Inhibitors OR Gliflozins OR Glucose Transporter Type 4 OR Solute Carrier Family 2, Facilitated Glucose Transporter, Member 4 Protein OR Glucose Transporter, Insulin-Responsive OR Insulin Responsive Glucose Transporter OR Insulin-Responsive Glucose Transporter OR GLUT-4 Protein OR GLUT 4 Protein OR SLC2A4 Protein OR GLUT4 Protein OR Deoxyglucose OR 2 Desoxy D glucose OR 2-Desoxy-D-glucose OR 2-Deoxy-D-glucose OR 2 Deoxy D glucose OR 2-Deoxyglucose OR 2 Deoxyglucose OR Glucose Transporter Type 1 OR Solute Carrier Family 2, Facilitated Glucose Transporter, Member 1 Protein OR GLUT 1 Protein OR GLUT-1 Protein OR Erythrocyte Glucose Transporter OR Glucose Transporter, Erythrocyte OR SLC2A1 Protein OR GLUT1 Protein OR Incretins OR Glucose-Dependent Insulin-Releasing Hormone OR Hormone, Glucose-Dependent Insulin-Releasing OR Glucose Dependent Insulin Releasing Hormone OR Insulin-Releasing Hormone, Glucose-Dependent OR Incretin Effect OR Incretin Effects OR Effects, Incretin OR Effect, Incretin OR Incretin OR Gastric Inhibitory Polypeptide OR Peptide, Glucose-Dependent Insulin-Releasing OR Glucose Dependent Insulin Releasing Peptide OR Glucose-Dependent Insulin-Releasing Peptide OR Insulin-Releasing Peptide, Glucose-Dependent OR Insulinotropic Peptide, Glucose-Dependent OR Peptide, Glucose-Dependent Insulinotropic OR Glucose-Dependent Insulinotropic Peptide OR Glucose Dependent Insulinotropic Peptide OR Gastric-Inhibitory Polypeptide OR Polypeptide, Gastric-Inhibitory OR Inhibitory Polypeptide, Gastric OR Polypeptide, Gastric Inhibitory OR Sodium-Glucose Transporter 2 OR Sodium Glucose Transporter 2 OR SGLT2 Protein OR SLC5A2 Protein OR Blood Glucose Self-Monitoring OR Sugar Self-Monitorings, Blood OR Sugar Self-Monitoring, Blood OR Self-Monitorings, Blood Glucose OR Blood Sugar Self Monitoring OR Blood Glucose Self-Monitorings OR Glucose, Blood, Self-Monitoring OR Glucose Self-Monitorings, Blood OR Blood Sugar Self-Monitorings OR Glucose, Blood, Self Monitoring OR Self-Monitoring, Blood Sugar OR Home Blood Glucose Monitoring OR Monitoring, Home Blood Glucose OR Glucose Self-Monitoring, Blood OR Blood Sugar Self-Monitoring OR Self Monitoring, Blood Glucose OR Self-Monitorings, Blood Sugar OR Self-Monitoring, Blood Glucose OR Blood Glucose Self

				Monitoring OR Glucosephosphate Dehydrogenase OR Dehydrogenase, Glucose-6-Phosphate OR Glucose 6 Phosphate Dehydrogenase OR Glucose-6-Phosphate Dehydrogenase OR Dehydrogenase, Glucosephosphate OR UTP-Glucose-1-Phosphate Uridylyltransferase OR UTP Glucose 1 Phosphate Uridylyltransferase OR Uridylyltransferase, UTP-Glucose-1-Phosphate OR UDP Glucose Pyrophosphorylase OR Pyrophosphorylase, UDP Glucose OR UDPG Pyrophosphorylase OR Uridylyltransferase, Glucosephosphate OR Glucosephosphate Uridylyltransferase OR Pyrophosphorylase, UDPG OR Adenosine Diphosphate Glucose OR Diphosphate Glucose, Adenosine OR Glucose, Adenosine Diphosphate OR Diphosphoglucose, Adenosine OR Pyrophosphateglucose, Adenosine OR ADP Glucose OR Adenosine Pyrophosphateglucose OR Adenosine Diphosphoglucose OR Glucose, ADP OR ADPG OR Glucose-1-Phosphate Adenylyltransferase OR Adenylyltransferase, Glucose-1-Phosphate OR Adenosine Diphosphate Glucose Pyrophosphorylase OR Glucose 1 Phosphate Adenylyltransferase OR Diphosphoglucose Pyrophosphorylase, Adenosine OR Synthase, ADP-Glucose OR ADP Glucose Pyrophosphorylase OR Pyrophosphorylase, ADP-Glucose OR ADP-Glucose Synthetase OR ADP-Glucose Pyrophosphorylase OR ADP-Glucose Synthase OR Adenosine Diphosphoglucose Pyrophosphorylase OR ADP Glucose Synthase OR ADP Glucose Synthetase OR Synthetase, ADP-Glucose OR Pyrophosphorylase, Adenosine Diphosphoglucose OR ADPG Synthetase OR ADPGlucose Pyrophosphorylase OR Pyrophosphorylase, ADPGlucose OR Synthetase, ADPG OR Glucose Clamp Technique OR Technique, Glucose Clamp OR Glucose Clamp Techniques OR Technics, Glucose Clamp OR Techniques, Glucose Clamp OR Glucose Clamp Technic OR Glucose Clamp Technics OR Technic, Glucose Clamp OR Clamping, Euglycaemic OR Clamping, Euglycemic OR Euglycemic Clamping OR Euglycaemic Clamping OR Glucose Clamping OR Clamping, Glucose OR Clamp, Glucose OR Glucose Clamp OR Clamp, Euglycaemic OR Glucose Clamps OR Euglycemic Clamp OR Euglycaemic Clamps OR Euglycemic Clamps OR Clamps, Euglycemic OR Clamps, Glucose OR Clamp, Euglycemic OR Clamps, Euglycaemic OR Euglycaemic Clamp OR Sodium-Glucose Transport Proteins OR Glucose-Sodium Transport System OR Sodium Glucose Transport Proteins OR Sodium Glucose Transport System OR Sodium-Glucose Transport System OR Glucose Sodium Transport System OR Sodium-Sugar Transporter OR Sodium Sugar Transporter OR Transporter, Sodium-Sugar OR Sodium Glucose Transporters OR Glucose Transporters, Sodium OR Glucose Cotransporters, Sodium OR Sodium Glucose Cotransporters OR SGLT Proteins OR Glucans OR Glucose Polymer OR Polymer, Glucose OR Glucan (BO) OR Polyglucoses OR Polycose OR Uridine Diphosphate Glucose Dehydrogenase OR Glucose Dehydrogenase, UDP OR Dehydrogenase, UDP Glucose OR UDP Glucose Dehydrogenase OR Dehydrogenase, UDPG OR UDPG Dehydrogenase OR Glucose Transport Proteins, Facilitative OR Glucose Transport Facilitators OR Glucose Transport Protein OR SLC2A Proteins OR GLUT Proteins OR Glucose Transporter OR Glucose Dehydrogenases OR Oxidoreductases, Glucose OR Glucose Oxidoreductases OR Dehydrogenases, Glucose OR Glucose Oxidase OR Oxidase, Glucose OR Microcid OR Phosphoglucomutase OR Phosphomutase, Glucose OR Glucose Phosphomutase OR Glucose 1-Dehydrogenase OR Glucose 1 Dehydrogenase OR Dehydrogenase, Glucose OR Glucose Dehydrogenase OR Glucose OR Glucose, (beta-D)-Isomer OR Glucose, (alpha-D)-Isomer OR Glucose, (DL)-Isomer OR Glucose, (L)-Isomer OR D Glucose OR D-Glucose OR L Glucose OR L-Glucose OR Dextrose, Anhydrous OR Anhydrous Dextrose OR Monohydrate, Glucose OR Glucose Monohydrate OR Dextrose OR Glucose Intolerance OR Glucose Tolerances, Impaired OR Tolerances, Impaired Glucose OR Tolerance, Impaired Glucose OR Impaired Glucose Tolerances OR Glucose Tolerance, Impaired OR Impaired Glucose Tolerance OR Intolerances, Glucose OR Intolerance, Glucose OR Glucose Intolerances OR Glucose

				Metabolism Disorders OR Glucose Metabolic Disorders OR Glucose Metabolic Disorder OR Metabolism Disorder, Glucose OR Disorders, Glucose Metabolism OR Glucose Metabolism Disorder OR Disorder, Glucose Metabolism OR Metabolic Disorder, Glucose OR Disorders, Glucose Metabolic OR Disorder, Glucose Metabolic OR Metabolism Disorders, Glucose OR Metabolic Disorders, Glucose OR Glucose Solution, Hypertonic OR Glucose Hypertonic Solution OR Hypertonic Solutions, Glucose OR Solution, Glucose Hypertonic OR Hypertonic Solution, Glucose OR Solutions, Hypertonic Glucose OR Hypertonic Glucose Solution OR Solution, Hypertonic Glucose OR Solutions, Glucose Hypertonic OR Glucose Hypertonic Solutions OR Hypertonic Glucose Solutions OR Glucose Solutions, Hypertonic OR Glucose-6-Phosphatase OR Glucose-6-Phosphate Phosphohydrolase OR Glucose 6 Phosphatase OR Glucose 6-Phosphatase OR Glucosephosphatase OR Blood Glucose OR Glucose, Blood OR Sugar, Blood OR Blood Sugar OR Glucose-6-Phosphate OR Glucose 6 Phosphate OR Uridine Diphosphate Glucose OR Glucose, Uridine Diphosphate OR Diphosphate Glucose, Uridine OR UDP Glucose OR Diphosphoglucose, Uridine OR Uridine Diphosphoglucose OR Glucose, UDP OR UDPG OR Glucose Tolerance Test OR Intravenous Glucose Tolerance Test OR Oral Glucose Tolerance Test OR Intravenous Glucose Tolerance OR Glucose Tolerance, Oral OR Oral Glucose Tolerance OR Glucose Tolerance Tests OR OGTT OR Sodium-Glucose Transporter 1 OR Sodium Glucose Transporter 1 OR Sodium-Glucose Cotransporter 1 OR Sodium Glucose Cotransporter 1 OR SLC5A1 Protein OR SGLT1 Protein) (Glutamine-Fructose-6-Phosphate Transaminase OR 2-Amino-2-Deoxy-D-Glucose-6-Phosphate Ketol-Isomerase OR 2 Amino 2 Deoxy D Glucose 6 Phosphate Ketol Isomerase OR Ketol-Isomerase, 2-Amino-2-Deoxy-D-Glucose-6-Phosphate OR Glutamine-Fructose-6-Phosphate Transaminase OR Glutamine Fructose 6 P Aminotransferase OR Glutamine-Fructose-6-P Aminotransferase OR Glutamine-Fructose-6-Phosphate Aminotransferase OR Aminotransferase, Glutamine-Fructose-6-P OR Glutamine Fructose 6 Phosphate Aminotransferase OR Aminotransferase, Glutamine-Fructose-6-Phosphate OR Glucosaminephosphate Isomerase OR Glucosamine 6 Phosphate Synthetase OR Glucosamine-6-Phosphate Synthase OR Glutamine:Fructose-6-Phosphate-Amidotransferase OR Glucosamine 6 Phosphate Synthase OR Glucosaminephosphate Isomerase OR Glucosamine 6-Phosphate Synthetase OR 6-Phosphate Synthetase, Glucosamine OR Glutamine:Fructose 6 Phosphate Amidotransferase OR Aminotransferase, Hexosephosphate OR Hexosephosphate Aminotransferase OR Glucosamine Synthetase) OR Starch Synthase OR ADP Glucose Starch Glucosyltransferase OR Granule Bound Starch Synthase OR Synthase, Granule-Bound Starch OR Granule-Bound Starch Synthase OR Starch (Bacterial Glycogen) Synthase OR Starch Synthase, Granule-Bound OR Synthase, Starch OR GBSS OR Fluorodeoxyglucose F18 OR 2 Fluoro 2 deoxy D glucose OR 2-Fluoro-2-deoxy-D-glucose OR 2-Fluoro-2-deoxyglucose OR 2 Fluoro 2 deoxyglucose OR Fluorodeoxyglucose F 18 OR Fludeoxyglucose F 18 OR F 18, Fluorodeoxyglucose OR Fluorine-18-fluorodeoxyglucose OR Fluorine 18 fluorodeoxyglucose OR F 18, Fludeoxyglucose OR 18F Fluorodeoxyglucose OR Fluorodeoxyglucose, 18F OR 18F-FDG OR F18, Fluorodeoxyglucose OR 18FDG OR Glucose Transporter Type 5 OR GLUT 5 Protein OR GLUT-5 Protein OR D-Fructose Transporter OR GLUT5 Protein OR SLC2A5 Protein OR Monosaccharide Transport Proteins OR Erythrocyte Band 4.5 Protein OR Transport-Inducing Protein, Glucose OR Glucose Transport Inducing Protein OR Glucose Transport-Inducing Protein OR 4.5 Preactin, Band OR Band 4.5 Preactin OR Preactin, Band 4.5 OR Proteins, Monosaccharide Transport OR Transport Proteins, Monosaccharide OR Transport Proteins, Hexose OR Hexose Transport Proteins OR Hexose Transporter OR Glycogen Storage Disease Type I OR Glycogen Storage Disease 1 (GSD I) OR Deficiency, Glucose-6-Phosphatase OR Glucose-6-

				Phosphatase Deficiency OR Deficiencies, Glucose-6-Phosphatase OR Glucose-6-Phosphatase Deficiencies OR Glucose 6 Phosphatase Deficiency OR Hepatorenal Glycogen Storage Disease OR Disease, von Gierke's OR von Gierke Disease OR Disease, von Gierke OR von Gierke's Disease OR von Gierkes Disease OR Gierkes Disease OR Disease, Gierke's OR Glycogenosis 1 OR Gierke's Disease OR Deficiencies, Glucosephosphatase OR Deficiency, Glucosephosphatase OR Gierke Disease OR Glucosephosphatase Deficiencies OR Glucosephosphatase Deficiency OR Disease, Gierke OR Glycogen Synthase OR UDP Glucose Glycogen Glucosyl Transferase OR UDP-Glucose Glycogen Glucosyl Transferase OR Glycogen Synthase I OR Glycogen (Starch) Synthase OR Synthase D OR Glycogen Synthetase OR Synthase, Glycogen OR Synthetase, Glycogen OR Synthase I OR Acetylglucosamine OR 2 Acetamido 2 Deoxy D Glucose OR 2-Acetamido-2-Deoxy-D-Glucose OR N-Acetyl-D-Glucosamine OR N Acetyl D Glucosamine OR 2-Acetamido-2-Deoxyglucose OR 2 Acetamido 2 Deoxyglucose OR Glucose Transporter Type 3 OR Solute Carrier Family 2, Facilitated Glucose Transporter, Member 3 Protein OR GLUT 3 Protein OR GLUT-3 Protein OR GLUT3 Protein OR SLC2A3 Protein OR Glucose Transporter Type 2 OR Solute Carrier Family 2, Facilitated Glucose Transporter, Member 2 Protein OR GLUT-2 Protein OR GLUT 2 Protein OR SLC2A2 Protein OR GLUT2 Protein OR Streptozocin OR 2-Deoxy-2-((methylnitrosoamino)carbonyl)amino-D-glucose OR Streptozotocine OR Streptozotocin OR Zanosar OR Glucosephosphate Dehydrogenase Deficiency OR Deficiency of Glucose 6 Phosphate Dehydrogenase OR Hemolytic Anemia Due to G6PD Deficiency OR Deficiency of Glucose-6-Phosphate Dehydrogenase OR Dehydrogenase Deficiencies, Glucose-6-Phosphate OR Glucose 6 Phosphate Dehydrogenase Deficiency OR Deficiency, Glucose-6-Phosphate Dehydrogenase OR Glucose-6-Phosphate Dehydrogenase Deficiencies OR Deficiencies, Glucose-6-Phosphate Dehydrogenase OR Dehydrogenase Deficiency, Glucose-6-Phosphate OR Glucose-6-Phosphate Dehydrogenase Deficiency OR Glucosephosphate Dehydrogenase Deficiencies OR Deficiency, Glucosephosphate Dehydrogenase OR Dehydrogenase Deficiency, Glucosephosphate OR Deficiencies, Glucosephosphate Dehydrogenase OR Dehydrogenase Deficiencies, Glucosephosphate OR Deficiency, GPD OR G6PD Deficiency OR Deficiencies, GPD OR Deficiencies, G6PD OR Deficiency, G6PD OR G6PD Deficiencies OR GPD Deficiency OR GPD Deficiencies OR Glucose-6-Phosphate Isomerase OR Tumor Cell Autocrine Motility Factor OR Tumor-Cell Autocrine Motility Factor OR Tumor Autocrine Motility Factor OR Isomerase, Glucose 6 Phosphate OR Glucose 6 Phosphate Isomerase OR Isomerase, Glucose-6-Phosphate OR Motility Factor, Autocrine OR Autocrine Motility Factor OR Phosphohexose Isomerase OR Phosphoglucose Isomerase OR Glucosephosphate Isomerase OR Isomerase, Phosphoglucose OR Isomerase, Glucosephosphate OR Isomerase, Phosphohexose OR Neuroleukin OR High Fructose Corn Syrup OR High Fructose Maize Syrup OR High-Fructose Maize Syrup OR Syrup, High-Fructose Maize OR Maize Syrup, High-Fructose OR Glucose-Fructose Syrup OR Glucose Fructose Syrup OR Syrup, Glucose-Fructose OR Corn Sugar OR Syrup, Maize OR Maize Syrup OR Sugar, Corn OR Isoglucose OR UDPglucose 4-Epimerase AND 4-Epimerase, UDP-Glucose OR UDP Glucose 4 Epimerase OR UDP-Glucose 4-Epimerase OR UDP-Galactose 4-Epimerase OR UDP Galactose 4 Epimerase OR 4-Epimerase, UDP-Galactose OR Uridine Diphosphate Glucose Epimerase OR UDPgalactose 4 Epimerase OR Epimerase, UDP Glucose OR 4-Epimerase, UDPgalactose OR UDPglucose 4 Epimerase OR Galactose Epimerase, UDP OR UDP Glucose Epimerase OR 4-Epimerase, UDPglucose OR Glucose Epimerase, UDP OR UDPgalactose 4-Epimerase OR Epimerase, UDP Galactose OR UDP Galactose Epimerase OR 3-O-Methylglucose OR 3-O-Methyl-D-Glucose OR 3 O Methyl D Glucose OR 3 O Methylglucose OR Sodium-Glucose Transporter 2 Inhibitors OR Sodium Glucose Transporter 2 Inhibitors OR SGLT-2 Inhibitors

				OR SGLT 2 Inhibitors OR SGLT2 Inhibitors OR Gliflozins OR Glucose Transporter Type 4 OR Solute Carrier Family 2, Facilitated Glucose Transporter, Member 4 Protein OR Glucose Transporter, Insulin-Responsive OR Insulin Responsive Glucose Transporter OR Insulin-Responsive Glucose Transporter OR GLUT-4 Protein OR GLUT 4 Protein OR SLC2A4 Protein OR GLUT4 Protein OR Deoxyglucose OR 2 Desoxy D glucose OR 2-Desoxy-D-glucose OR 2-Deoxy-D-glucose OR 2 Deoxy D glucose OR 2-Deoxyglucose OR 2 Deoxyglucose OR Glucose Transporter Type 1 OR Solute Carrier Family 2, Facilitated Glucose Transporter, Member 1 Protein OR GLUT 1 Protein OR GLUT-1 Protein OR Erythrocyte Glucose Transporter OR Glucose Transporter, Erythrocyte OR SLC2A1 Protein OR GLUT1 Protein OR Incretins OR Glucose-Dependent Insulin-Releasing Hormone OR Hormone, Glucose-Dependent Insulin-Releasing OR Glucose Dependent Insulin Releasing Hormone OR Insulin-Releasing Hormone, Glucose-Dependent OR Incretin Effect OR Incretin Effects OR Effects, Incretin OR Effect, Incretin OR Incretin OR Gastric Inhibitory Polypeptide OR Peptide, Glucose-Dependent Insulin-Releasing OR Glucose Dependent Insulin Releasing Peptide OR Glucose-Dependent Insulin-Releasing Peptide OR Insulin-Releasing Peptide, Glucose-Dependent OR Insulinotropic Peptide, Glucose-Dependent OR Peptide, Glucose-Dependent Insulinotropic OR Glucose-Dependent Insulinotropic Peptide OR Glucose Dependent Insulinotropic Peptide OR Gastric-Inhibitory Polypeptide OR Polypeptide, Gastric-Inhibitory OR Inhibitory Polypeptide, Gastric OR Polypeptide, Gastric Inhibitory OR Sodium-Glucose Transporter 2 OR Sodium Glucose Transporter 2 OR SGLT2 Protein OR SLC5A2 Protein OR Blood Glucose Self-Monitoring OR Sugar Self-Monitorings, Blood OR Sugar Self-Monitoring, Blood OR Self-Monitorings, Blood Glucose OR Blood Sugar Self Monitoring OR Blood Glucose Self-Monitorings OR Glucose, Blood, Self-Monitoring OR Glucose Self-Monitorings, Blood OR Blood Sugar Self-Monitorings OR Glucose, Blood, Self Monitoring OR Self-Monitoring, Blood Sugar OR Home Blood Glucose Monitoring OR Monitoring, Home Blood Glucose OR Glucose Self-Monitoring, Blood OR Blood Sugar Self-Monitoring OR Self Monitoring, Blood Glucose OR Self-Monitorings, Blood Sugar OR Self-Monitoring, Blood Glucose OR Blood Glucose Self Monitoring OR Glucosephosphate Dehydrogenase OR Dehydrogenase, Glucose-6-Phosphate OR Glucose 6 Phosphate Dehydrogenase OR Glucose-6-Phosphate Dehydrogenase OR Dehydrogenase, Glucosephosphate OR UTP-Glucose-1-Phosphate Uridylyltransferase OR UTP Glucose 1 Phosphate Uridylyltransferase OR Uridylyltransferase, UTP-Glucose-1-Phosphate OR UDP Glucose Pyrophosphorylase OR Pyrophosphorylase, UDP Glucose OR UDPG Pyrophosphorylase OR Uridylyltransferase, Glucosephosphate OR Glucosephosphate Uridylyltransferase OR Pyrophosphorylase, UDPG OR Adenosine Diphosphate Glucose OR Diphosphate Glucose, Adenosine OR Glucose, Adenosine Diphosphate OR Diphosphoglucose, Adenosine OR Pyrophosphateglucose, Adenosine OR ADP Glucose OR Adenosine Pyrophosphateglucose OR Adenosine Diphosphoglucose OR Glucose, ADP OR ADPG OR Glucose-1-Phosphate Adenylyltransferase OR Adenylyltransferase, Glucose-1-Phosphate OR Adenosine Diphosphate Glucose Pyrophosphorylase OR Glucose 1 Phosphate Adenylyltransferase OR Diphosphoglucose Pyrophosphorylase, Adenosine OR Synthase, ADP-Glucose OR ADP Glucose Pyrophosphorylase OR Pyrophosphorylase, ADP-Glucose OR ADP-Glucose Synthetase OR ADP-Glucose Pyrophosphorylase OR ADP-Glucose Synthase OR Adenosine Diphosphoglucose Pyrophosphorylase OR ADP Glucose Synthase OR ADP Glucose Synthetase OR Synthetase, ADP-Glucose OR Pyrophosphorylase, Adenosine Diphosphoglucose OR ADPG Synthetase OR ADPGlucose Pyrophosphorylase OR Pyrophosphorylase, ADPGlucose OR Synthetase, ADPG OR Glucose Clamp Technique OR Technique, Glucose Clamp OR Glucose Clamp Techniques OR Technics, Glucose Clamp OR Techniques, Glucose Clamp OR Glucose Clamp Technic OR Glucose Clamp Technics OR Technic, Glucose

				Clamp OR Clamping, Euglycaemic OR Clamping, Euglycemic OR Euglycemic Clamping OR Euglycaemic Clamping OR Glucose Clamping OR Clamping, Glucose OR Clamp, Glucose OR Glucose Clamp OR Clamp, Euglycaemic OR Glucose Clamps OR Euglycemic Clamp OR Euglycaemic Clamps OR Euglycemic Clamps OR Clamps, Euglycemic OR Clamps, Glucose OR Clamp, Euglycemic OR Clamps, Euglycaemic OR Euglycaemic Clamp OR Sodium-Glucose Transport Proteins OR Glucose-Sodium Transport System OR Sodium Glucose Transport Proteins OR Sodium Glucose Transport System OR Sodium-Glucose Transport System OR Glucose Sodium Transport System OR Sodium-Sugar Transporter OR Sodium Sugar Transporter OR Transporter, Sodium-Sugar OR Sodium Glucose Transporters OR Glucose Transporters, Sodium OR Glucose Cotransporters, Sodium OR Sodium Glucose Cotransporters OR SGLT Proteins OR Glucans OR Glucose Polymer OR Polymer, Glucose OR Glucan (BO) OR Polyglucoses OR Polycose OR Uridine Diphosphate Glucose Dehydrogenase OR Glucose Dehydrogenase, UDP OR Dehydrogenase, UDP Glucose OR UDP Glucose Dehydrogenase OR Dehydrogenase, UDPG OR UDPG Dehydrogenase OR Glucose Transport Proteins, Facilitative OR Glucose Transport Facilitators OR Glucose Transport Protein OR SLC2A Proteins OR GLUT Proteins OR Glucose Transporter OR Glucose Dehydrogenases OR Oxidoreductases, Glucose OR Glucose Oxidoreductases OR Dehydrogenases, Glucose OR Glucose Oxidase OR Oxidase, Glucose OR Microcid OR Phosphoglucomutase OR Phosphomutase, Glucose OR Glucose Phosphomutase OR Glucose 1-Dehydrogenase OR Glucose 1 Dehydrogenase OR Dehydrogenase, Glucose OR Glucose Dehydrogenase OR Glucose OR Glucose, (beta-D)-Isomer OR Glucose, (alpha-D)-Isomer OR Glucose, (DL)-Isomer OR Glucose, (L)-Isomer OR D Glucose OR D-Glucose OR L Glucose OR L-Glucose OR Dextrose, Anhydrous OR Anhydrous Dextrose OR Monohydrate, Glucose OR Glucose Monohydrate OR Dextrose OR Glucose Intolerance OR Glucose Tolerances, Impaired OR Tolerances, Impaired Glucose OR Tolerance, Impaired Glucose OR Impaired Glucose Tolerances OR Glucose Tolerance, Impaired OR Impaired Glucose Tolerance OR Intolerances, Glucose OR Intolerance, Glucose OR Glucose Intolerances OR Glucose Metabolism Disorders OR Glucose Metabolic Disorders OR Glucose Metabolic Disorder OR Metabolism Disorder, Glucose OR Disorders, Glucose Metabolism OR Glucose Metabolism Disorder OR Disorder, Glucose Metabolism OR Metabolic Disorder, Glucose OR Disorders, Glucose Metabolic OR Disorder, Glucose Metabolic OR Metabolism Disorders, Glucose OR Metabolic Disorders, Glucose OR Glucose Solution, Hypertonic OR Glucose Hypertonic Solution OR Hypertonic Solutions, Glucose OR Solution, Glucose Hypertonic OR Hypertonic Solution, Glucose OR Solutions, Hypertonic Glucose OR Hypertonic Glucose Solution OR Solution, Hypertonic Glucose OR Solutions, Glucose Hypertonic OR Glucose Hypertonic Solutions OR Hypertonic Glucose Solutions OR Glucose Solutions, Hypertonic OR Glucose-6-Phosphatase OR Glucose-6-Phosphate Phosphohydrolase OR Glucose 6 Phosphatase OR Glucose 6-Phosphatase OR Glucosephosphatase OR Blood Glucose OR Glucose, Blood OR Sugar, Blood OR Blood Sugar OR Glucose-6-Phosphate OR Glucose 6 Phosphate OR Uridine Diphosphate Glucose OR Glucose, Uridine Diphosphate OR Diphosphate Glucose, Uridine OR UDP Glucose OR Diphosphoglucose, Uridine OR Uridine Diphosphoglucose OR Glucose, UDP OR UDPG OR Glucose Tolerance Test OR Intravenous Glucose Tolerance Test OR Oral Glucose Tolerance Test OR Intravenous Glucose Tolerance OR Glucose Tolerance, Oral OR Oral Glucose Tolerance OR Glucose Tolerance Tests OR OGTT OR Sodium-Glucose Transporter 1 OR Sodium Glucose Transporter 1 OR Sodium-Glucose Cotransporter 1 OR Sodium Glucose Cotransporter 1 OR SLC5A1 Protein OR SGLT1 Protein)
PubMed	(blood glucose[MeSH Terms] OR	2005-01-01 to	None	((Glucose OR D-Glucose OR D Glucose OR Dextrose OR Glucose, (alpha-D)-Isomer OR Anhydrous Dextrose OR Dextrose, Anhydrous OR Glucose, (DL)-Isomer OR Glucose, (L)-Isomer

	hyperglycemia[MeSH Terms]) AND stroke[MeSH Terms]	2019-08-01		OR L-Glucose OR L Glucose OR Glucose Monohydrate OR Monohydrate, Glucose OR Glucose, (beta-D)-Isomer) OR (Hyperglycemia OR Hyperglycemias OR Hyperglycemia, Postprandial OR Hyperglycemias, Postprandial OR Postprandial Hyperglycemias OR Postprandial Hyperglycemia) AND (Stroke OR Strokes OR Cerebrovascular Accident OR Cerebrovascular Accidents OR CVA OR CVAs OR Cerebrovascular Apoplexy OR Apoplexy, Cerebrovascular OR Vascular Accident, Brain OR Brain Vascular Accident OR Brain Vascular Accidents OR Vascular Accidents, Brain OR Cerebrovascular Stroke OR Cerebrovascular Strokes OR Stroke, Cerebrovascular OR Strokes, Cerebrovascular OR Apoplexy OR Cerebral Stroke OR Cerebral Strokes OR Stroke, Cerebral OR Strokes, Cerebral OR Stroke, Acute OR Acute Stroke OR Acute Strokes OR Strokes, Acute OR Cerebrovascular Accident, Acute OR Acute Cerebrovascular Accident OR Acute Cerebrovascular Accidents OR Cerebrovascular Accidents, Acute)
EMBASE	Emtree-major focus exp. Hyperglycemia OR Emtree-major focus exp. Glucose blood level AND Emtree-major focus exp. Cerebrovascular accident	2017-01-01 to 2019-08-01	None	(hyperglycemia OR glucose blood level, elevated OR glycemia, hyper OR hyperglucemia OR hyperglycaemia OR hyperglycemic syndrome) OR (cartose OR corn sugar OR d glucose OR dextro glucose OR dextropur OR dextrose OR dextrose 10% OR dextrose 2.5% OR dextrose 20% OR dextrose 25% OR dextrose 30% OR dextrose 38.5% OR dextrose 40% OR dextrose 5% OR dextrose 50% OR dextrose 60% OR dextrose 7.7% OR dextrose 70% OR dextrosol OR glucodin OR glucola OR glucolin OR glucose hypotonic solution OR glucose influx OR glucose medium OR glucose solution OR glucose solution, hypertonic OR glutol OR glycose OR glycovarin OR grape sugar OR hypertonic dextrose solution OR hypertonic glucose solution OR hypotonic glucose OR hypotonic glucose solution OR koladex OR saccharum amylaceum OR starch sugar OR vamin glucose) AND cerebrovascular accident OR accident, cerebrovascular OR acute cerebrovascular lesion OR acute focal cerebral vasculopathy OR acute stroke OR apoplectic stroke OR apoplexia OR apoplexy OR blood flow disturbance, brain OR brain accident OR brain attack OR brain blood flow disturbance OR brain insult OR brain insultus OR brain ischaemic attack OR brain ischemic attack OR brain vascular accident OR cerebral apoplexia OR cerebral insult OR cerebral stroke OR cerebral vascular accident OR cerebral vascular insufficiency OR cerebro vascular accident OR cerebrovascular arrest OR cerebrovascular failure OR cerebrovascular injury OR cerebrovascular insufficiency OR cerebrovascular insult OR cerebrum vascular accident OR cryptogenic stroke OR CVA OR ischaemic cerebral attack OR ischaemic seizure OR ischemic cerebral attack OR ischemic seizure OR stroke

Supplementary Table 2. Characteristics of included studies (PICOs).

Citation	Patient population	Intervention	Comparison	Outcomes
Azevedo et al. 2009[16]	Inclusion Criteria Patients admitted to a general ICU with acute ischemic stroke. Exclusion Criteria Not specified.	Continuous IV insulin infusion to maintain blood glucose levels <140 mg/dl	IV hydration with a glucose-free solution (Ringer III) and enteral nutritional formula containing 33.3% carbohydrates. Regular insulin SC to maintain blood glucose levels below 150 mg/dl.	Primary Outcomes NIH Stroke Scale Extended Glasgow Outcome Scale
Bruno et al. 2013[13]	Inclusion Criteria Neuroimaging excluding other causes	Continuous IV insulin infusion to maintain glucose levels of 90 to 130 mg/dl.	SC regular insulin sliding scale administered QID as needed. .	Primary Outcomes Mean glucose difference between the 2 groups during protocol treatment.

	of acute neurological deterioration. Onset of symptoms within 12 hours before randomization. Baseline blood glucose level ≥8.3 mmol/L (≥150 mg/dl) Baseline NIHSS score of 3 to 22, with at least 2 points on the motor portion <u>Exclusion Criteria</u> Preexisting incapacitating illness equivalent to a modified Rankin Scale score ≥3. Indication for intravenous insulin therapy due to myocardial infarction or diabetic ketoacidosis. Corticosteroid therapy.	Diabetic patients received additional SC very rapidly acting insulin immediately after each meal, 1 U for each 20 g of carbohydrate consumed.	No insulin was given when glucose value was <200 mg/dl. Diabetic patients received additional SC regular insulin immediately after each meal at 0.12 U/kg.	Hypoglycemia defined as any glucose value <60 mg/dL and any associated symptoms during protocol treatment. <u>Secondary Outcomes</u> Favorable clinical outcome defined as a modified Rankin Scale score ≤2, modified Barthel Index score of 19 to 20, an NIHSS score ≤2, and the Stroke-Specific Quality of Life scale at 3 months.
Gray et al. 2007[22]	<u>Inclusion Criteria</u> Fixed neurological deficit with no evidence of rapid improvement during a 60 min period after onset. <u>Exclusion Criteria</u> Subarachnoid hemorrhage Isolated posterior circulation syndromes with no physical disability Pure language disorders Renal failure (urea >20 mmol/L or creatinine >200 μmol/L) Anemia (hemoglobin <9 g/dl) Coma (motor response ≤3 on the Glasgow coma scale) Insulin treated diabetes mellitus Previous disabling stroke	Continuous IV Glucose Potassium Insulin infusion (500 mL of 10% dextrose and 20 mmol potassium chloride plus insulin adjusted prn) for a minimum of 24 h to maintain capillary blood glucose concentration at 72 - 126 mg/dL	0·9% normal saline (154 mmol/L sodium) at 100 mL/h for 24 h with capillary glucose monitoring every 2 h.	<u>Primary Outcome</u> All-cause mortality at 90 days <u>Secondary Outcomes</u> Avoidance of death or severe disability (mRS score 4-6) at 90 days Residual disability/neurological or functional recovery. Serum glucose concentration. Recurrent stroke Cardiac failure/myocardial infarction. Treated chest or urinary infection Plasma sodium concentration Plasma potassium concentration Hypoglycemia defined as <72 mg/dL for >30 minutes.

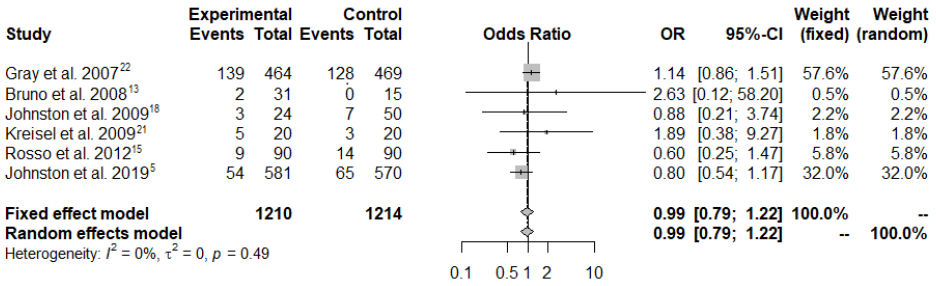
	Established history of dementia or abbreviated mental test score <7/10 Symptomatic cardiac failure			
Johnston et al. 2009[18]	Inclusion criteria >17 years old with ischemic stroke onset within 24 hours Glucose >110 mg/dl Able to be treated within 2 hours Exclusion criteria Renal dysfunction (creatinine ≥2.5 mg/dL) Confounding illness Experimental therapy for the enrollment stroke Pregnancy Life-threatening condition limiting follow-up Missing stratification information Standard care indication for insulin infusion	Insulin in normal saline (1 U/1 ml) as a continuous infusion guided by the eProtocol-insulin electronic support system PLUS Subcutaneous Humalog 1UI/15 g carbohydrate during meals to maintain a target glucose concentration of 70 – 110 mg/dL for 5 days or until discharge.	nsulin in normal saline (1 U/1 ml) as a continuous infusion guided by the eProtocol-insulin electronic support system PLUS Subcutaneous Humalog 1UI/15 g carbohydrate during meals to maintain a target glucose concentration of 70 – 200 mg/dL for 5 days or until discharge.	Primary Outcomes Hypoglycemia (<55 mg/dL) Symptomatic hypoglycemia Feasibility of glucose control (2 of 3 glucose concentrations closest to 24 hrs. within targeted range).
Johnston et al. 2019[5]	Inclusion criteria ≥18 years old Hyperglycemia (>110 mg/dL in diabetics or >150 mg/dL in non-diabetics) Acute ischemic stroke NIHSS score of 3 to 22 Presenting within 12 hours from stroke onset Exclusion Criteria Type 1 diabetes mellitus On renal dialysis Clinical indication for insulin infusion Condition that would confound assessment of the stroke clinical outcome	Continuous IV insulin infusion guided by a computer decision tool as needed to maintain a blood glucose concentration of 80 to 130 mg/dl PLUS Rapid acting SC insulin 20 minutes before meals	Insulin on a sliding scale administered SC every 6 hours as needed to maintain blood glucose concentration of 80 to 179 mg/dl PLUS Continuous IV saline solution for blinding	Primary outcomes Favorable modified Rankin Scale score (0-2 depending on baseline NIHSS) within 90 days Secondary outcomes 90-day NIHSS score 90-day Barthel Index score 90-day Stroke Specific Quality of Life score Lack of severe hypoglycemia defined as a glucose level <40 mg/dL
Kreisel et al. 2009[21]	Inclusion criteria Ischemic stroke with onset <24 hours	IV insulin solution (50 IU normal insulin in 50 ml 0.9% saline solution) controlled	SC short-acting regular insulin guided by a prespecified protocol to maintain	Primary outcomes Survival Rankin Scale

	Stable clinical deficits over at least 3 hours CT scan and/or MRI excluding other symptomatic causes for acute-onset focal neurological deficits <u>Exclusion Criteria</u> < 18 years old Pregnancy NIHSS score of <4 Expected survival time of less than 7 days Premorbid condition that might have compromised evaluation and treatment	by an electronic pump to maintain blood glucose concentrations 80-100 mg/dL.	blood glucose concentrations <200 mg/dL.	<u>Secondary outcomes</u> Hypoglycemia (<60 mg/dL) Severe hyperglycemia (>300 mg/dL) Death Good outcome (mRS 0-1)
Staszewski et al. 2011[14]	<u>Inclusion criteria</u> CT confirming ischemic etiology Non-diabetic Patients treated within 12 hours of stroke onset Age 50-80 years Modified Rankin Scale score ≥2 NIHSS score ≤1 No planned thrombolytic treatment <u>Exclusion Criteria</u> Admission hemoglobin A1c >6% Established diabetes Heart failure Renal failure Dementia Previous stroke	24-hour IV insulin infusion adjusted to maintain a glucose level of 81-126 mg/dL	SC insulin if plasma glucose level >180 mg/dL	<u>Primary outcomes</u> Symptomatic hypoglycemia (<60 mg/dL PLUS symptoms) Asymptomatic hypoglycemia (not specified) Maintenance of euglycemia; <u>Secondary outcomes</u> Mortality Functional outcome after 24 hours and at 30 days (mRS and NIHSS) Favorable outcome (mRS ≤2)
Rosso et al. 2012[15]	<u>Inclusion criteria</u> Ischemic stroke in the carotid territory (as per DWI) Initial MRI with DWI <5 hours of stroke onset Initiation of insulin treatment within 1 hour of MRI Admission NIHSS score 5-25 <u>Exclusion Criteria</u>	Soluble human Actrapid insulin IV continuous infusion with hourly dose adaptation stopped when achieving <100 mg/dL	SC insulin administered every 4 hours based stopped when achieving 145 mg/dL	<u>Primary outcome</u> Blood glucose levels <u>Secondary outcomes</u> Infarct volume and recanalization (per MRI days 1-3) Modified Rankin Scale at discharge and at 90 days Good outcome (mRS 0-2) NIHSS scale Death Hypoglycemia (<54 mg/dL)

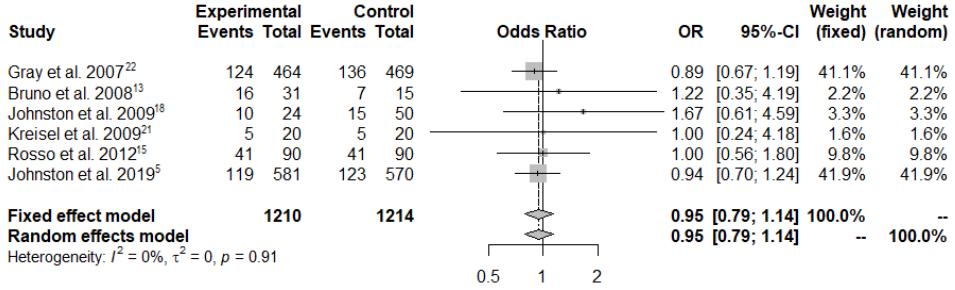
	Life-threatening conditions that limited follow-up Preadmission modified Rankin Scale >2 Patients under legal protection			
McCormick et al. 2010[20]	Inclusion Criteria >18 years old Acute hemispheric stroke <24 hours after onset Capillary blood glucose > 126 mg/dl Exclusion Criteria MRI not possible. Intracerebral hemorrhage	Glucose- Potassium-Insulin infusion (500ml 10% dextrose, 20 mmol potassium chloride, and 16 units of soluble recombinant human insulin) to maintain capillary blood glucose 72-126 mg/dl	IV 0.9% normal saline	Primary outcome Blood glucose concentration Blood pressure Infarct volume and recanalization (as per MRI days 3 & 7) Secondary outcomes NIHSS score at 7 days mRS at 30 days
Vinychuk et al. 2005[12]	Inclusion Criteria Admitted ≤12 h after developing symptoms Glucose levels in plasma >126 mg/dL Exclusion Criteria Acute myocardial infarction Acute or chronic renal failure Radiographically confirmed pneumonia Intracerebral or subarachnoid hemorrhage Presumable brain tumor Admitted to the clinic >24 hours after onset of stroke	Insulin-potassium-saline-magnesium infusion (400 ml of 0.9% NaCl, 40 ml of 3% KCl, 10 ml of 25% magnesium sulfate and short-action insulin) titrated according to a protocol to achieve a blood glucose level ≤126 mg/dL PLUS Standard therapy (see comparison)	Standard therapy (BP 160–180/90–100 mmHg, fluid and electrolyte balance, normalization of body temperature)	Primary outcome Plasma glucose concentration Secondary outcomes Barthel index Good outcome (Barthel index ≤50) NIHSS Scale
Vriesendrop et al. 2009[19]	Inclusion Criteria Acute neurological deficit from cerebral ischemia Onset less than 24 hours Exclusion Criteria Patients with previous insulin therapy	Predominantly basal insulin group: IV insulin adjusted hourly to achieve glucose concentration <110 mg/dL Predominantly meal related insulin: long acting insulin plus rapid acting insulin.	SC short action insulin if glucose concentration >300 mg/dL	Primary outcome Glucose concentration and AUC Secondary outcomes Hypoglycemia (<63 mg/dL)
Walters et al. 2006[17]	Inclusion Criteria <24 of onset of CT-confirmed ischemic stroke Venous blood glucose >145 mg/dL	IV infusion of insulin with dosage adjustment to maintain blood glucose 90 – 145 mg/dL.	Continuation of any pre-existing oral hypoglycemic therapy with intravenous	Primary outcome Mortality at 1 month Secondary outcomes NIHSS Score at baseline and at 1 month

	Glasgow coma scale >8 <u>Exclusion Criteria</u> Know diabetes mellitus requiring insulin Severe metabolic derangement Cardiac infarction Congestive heart failure		infusion (0.9% saline 8 5% glucose)	Hypoglycemia (<50 mg/dL)

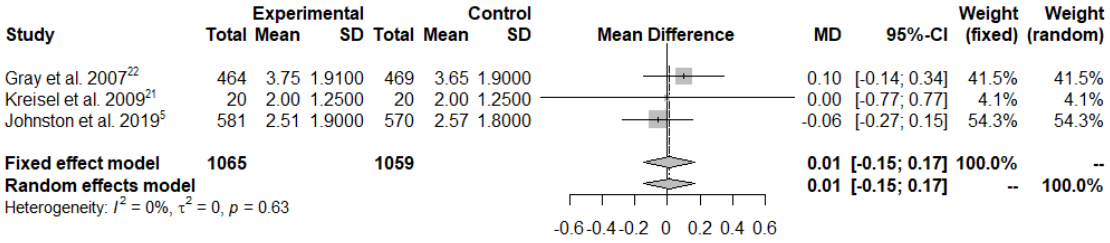
A



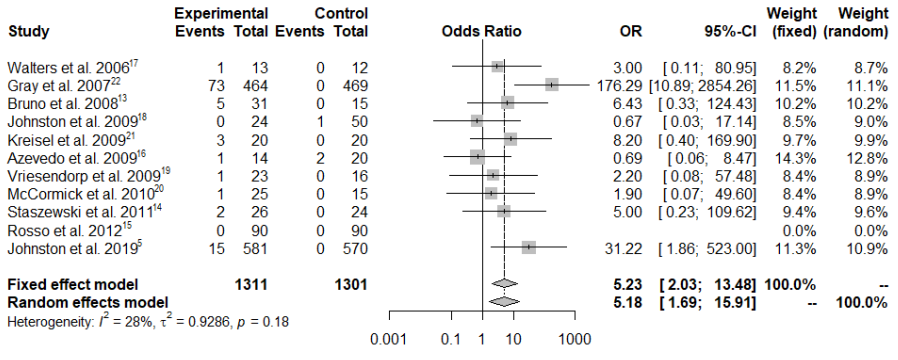
B



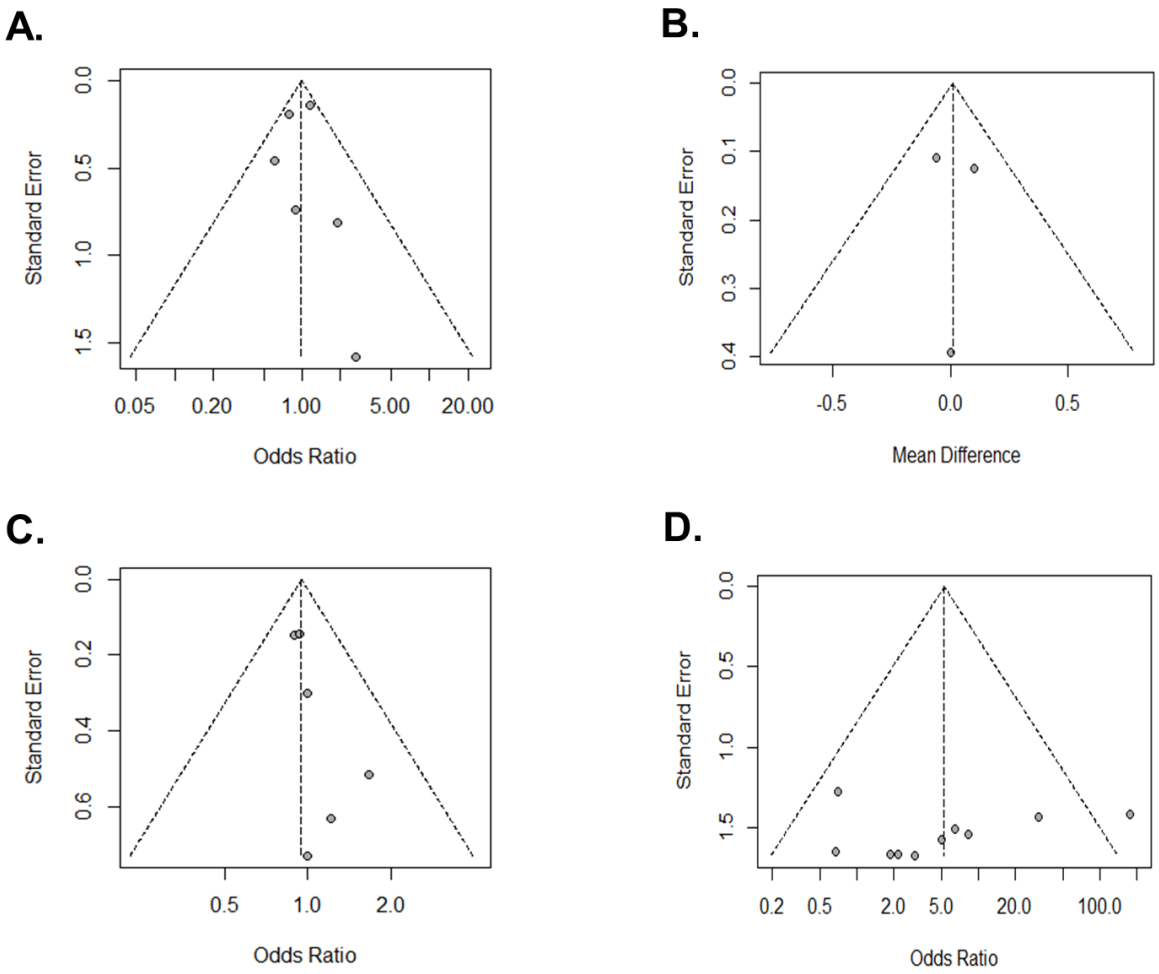
C



D



Supplementary Figure 1. Forest plots for A) mortality at ≥90 days of follow-up, B) independence at ≥90 days of follow-up, C) modified Rankin Scale score at ≥90 days of follow-up, and D) symptomatic or severe hypoglycemia during treatment.



Supplementary Figure 2. Funnel plots for A) mortality at ≥90 days of follow-up (p = 0.82), B) modified Rankin Scale score at ≥90 days of follow-up (p = 0.93), C) independence at ≥90 days of follow-up (p = 0.09), and D) symptomatic or severe hypoglycemia during treatment (p = 0.06).

Incidence and Outcomes of Acute Myocardial Infarction after Aneurysmal Subarachnoid Hemorrhage.

Christian D. Cerecedo-Lopez, MD[1]; Issac Ng[1], BSc; Hillary B. Nguyen, BA[1]; Pui Man Rosalind Lai[1], MD; William B. Gormley, MD, MPH, MBA[1], Nirav Patel, MD, MA[1], Kai U. Frerichs, MD[1], M. Ali Aziz-Sultan, MD, MBA[1], Rose Du, MD, PhD[1,*].

[1]Department of Neurosurgery, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA, USA.

***Corresponding Author.**

Rose Du, MD, PhD

Department of Neurosurgery

Brigham and Women's Hospital

75 Francis Street

Boston, MA 02115

Phone: 617-525-8132

Fax: 617-713-3050

Email: rdu@bwh.harvard.edu

ABSTRACT

Background: Myocardial injury occurs commonly after aneurysmal subarachnoid hemorrhage (aSAH). Precise estimates of the incidence of acute myocardial infarction (AMI) after aSAH are unavailable.

Objective: The purpose of this study was to estimate the incidence of AMI after aSAH and its association with clinical outcomes.

Methods: Adult patients with aSAH in the National Inpatient Samples (NIS) from 2002 to 2014 were included in the study. We estimated the annual incidence of AMI after aSAH and evaluated cardiovascular risk factors using univariate and multivariate logistic and linear regression models. Clinical outcomes assessed included functional status at discharge, in-patient mortality, length of stay, and total hospitalization cost adjusting for patient demographics and cardiovascular risk factors through an inverse probability weighted analysis. Subgroup analyses were further performed stratified by AMI type (ST segment elevation myocardial infarction [STEMI] vs. non-ST segment elevation myocardial infarction [NSTEMI]).

Results: 139,732 patients with aSAH were identified, 3.6% (95%CI: 3.3-3.9%) of which had AMI. NSTEMI was the most common type of AMI occurring after aSAH (70% vs. 30% for NSTEMI vs. STEMI, respectively). Risk factors associated with AMI were older age, female sex, and cardiovascular risk factors. AMI was also associated with poor functional status at discharge (OR: 2.27, 95% CI: 2.1 – 2.4, $p < 0.001$), higher in-hospital mortality (OR: 1.8, 95% CI: 1.7 – 19., $p <$

0.001), and a longer (MD: 3.84 days, 95% CI: 2.9 – 4.8 days, p = <0.001) and more costly (MD: $70,774, USD, 95% CI: $56,266, - $85,282, USD, p < 0.001) hospital stay.

Conclusion: AMI occurs in 3.6% of patients with aSAH and is associated with poor functional status at discharge, higher in-patient mortality, and a longer and more costly hospitalization.

INTRODUCTION

Myocardial injury can occur after any type of acute brain injury, but is most common after a subarachnoid hemorrhage, presenting in approximately 40% of all subarachnoid hemorrhage patients.[1,2] The incidence of myocardial injury after subarachnoid hemorrhage correlates directly with hemorrhage severity and is strongly associated with poor discharge disposition and high mortality.[2] The management of patients with myocardial injury often conflicts with the management of aneurysmal subarachnoid hemorrhage (aSAH), and complicates the care of aSAH patients.[3] Adequate management of myocardial injury after aSAH, however, is of paramount importance as acute myocardial infarction (AMI) after aSAH can lead to sudden death, cardiogenic shock, acute pulmonary edema or cardioembolic stroke, and is associated with poor outcomes after aSAH.[4–7]

Myocardial injury following aSAH can be due to ischemic or non-ischemic causes.[8] The management of non-ischemic causes of myocardial injury is aimed at optimizing care of the underlying causal diagnosis.[8] Conversely, the management of ischemic causes of myocardial injury is aimed at preservation of myocardial tissue, which is achieved through prompt reperfusion in AMI caused by a coronary thrombus (Type 1 AMI) or through physiologic parameter optimization in AMI caused by an imbalance of oxygen supply and demand (Type 2 AMI).[8] Precise estimates of the incidence of AMI after aSAH are unavailable, therefore, the National Inpatient Sample was utilized in this study to estimate the incidence of AMI after aSAH and its association with outcomes.

METHODS

Data Source

We used data from the National Inpatient Sample (NIS, Healthcare Cost and Utilization Project [HCUP], Agency for Healthcare Research and Quality).[9] The NIS is a sample of twenty percent of all discharges in non-federal hospitals.[9] Our institutional review board exempts studies utilizing the NIS from individual review. The NIS was formerly known as the Nationwide Inpatient Sample as its original design was aimed at providing information on all discharges from a sample of HCUP hospitals.[10] In 2012, the Nationwide Inpatient Sample was redesigned into the NIS, which is a sample of discharges from all HCUP hospitals.[10] To provide national-level estimates, analyses of the NIS must be weighted accounting for its complex survey design.[10] Trend weights, provided by HCUP, can be used in place of the former discharge weights for years prior to 2012 to provide national estimates.[10] We obtained trend weights for years 2002 – 2011 from HCUP and performed our analysis accounting for the complex survey design of the NIS.[11] In October of 2015 codes of the International Classification of Diseases (ICD) Version 10 were implemented across hospitals in the United States leading to a shift in the reporting of diseases.[12] Trend analysis combining ICD-9 and ICD-10 codes may lead to inaccurate estimates if discontinuity in the reporting of codes exist.[13] For this reason we limited our analysis of the NIS to years 2002 – 2014.

Inclusion and Exclusion Criteria

To select patients with aSAH we included individuals who: (1) had an International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis of subarachnoid hemorrhage (430) or intracerebral hemorrhage (431, 432.9), and (2) underwent microsurgical

clipping (ICD-9-CM procedure code: 39.51), coil embolization (39.72, 39.75, 39.76, 39.79), or other repair of aneurysm (39.52). Subsequently, included patients fulfilling any of the following criteria were excluded: (1) age less than 18 years old, (2) diagnosis of traumatic brain injury (800.0–801.9, 803.0–804.9, 850.0–854.1, 873.0–873.9), (3) diagnosis (747.81) or management (39.53, 92.30) of an arteriovenous malformation and/or fistula, or (4) a length of stay less than one day with an associated discharge to home.

Subarachnoid Hemorrhage Severity Grading

To account for the severity of subarachnoid hemorrhage in our analyses we estimated the NIS-SAH severity scale (NIS-SSS), which is a validated severity adjustment score for patients with aSAH in the NIS.[14] The NIS-SSS aims at providing a measurement of aSAH severity using the Hunt and Hess and World Federation of Neurosurgical Societies grading scales as templates. The NIS-SSS is obtained by assessing the presence of seven categories of findings available in the NIS that are suggestive of poor neurological status, low consciousness or focal neurological deficits: (1) diagnosis of coma (780.01, 780.03), (2) diagnosis of hydrocephalus (331.3, 331.4), (3) treatment of hydrocephalus (02.2, 02.31-02.39), (4) diagnosis of paresis/plegia (438.2-438.53), (5) cranial nerve deficits (378.5-378.56, 379.4-379.43), (6) diagnosis of aphasia (438.1-438.89), and (7) mechanical ventilation (96.04, 96.7-96.72). The presence of these categories of findings is then weighted by the contribution of each category to a poor functional outcome at discharge. We classified patients into poor grade on admission if they had a NIS-SSS value >7, which is suggestive of a Hunt and Hess grade in the III-V range.

Demographics and Cardiovascular Risk Factors

We obtained data on patient age, sex, payment type and hospital location and teaching status. We also obtained data on cardiovascular risk factors using codes described by Elixhauser et al.[15] Specifically, we obtain information on history of congestive heart failure (398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4 - 425.9, 428.x), cardiac arrythmias (426.0, 426.13, 426.7, 426.9, 426.10, 426.12, 427.0 - 427.4, 427.6 - 427.9, 785.0, 996.01, 996.04, V45.0, V53.3), valvular disease (093.2, 394.x - 397.x, 424.x, 746.3 - 746.6, V42.2, V43.3), pulmonary circulation disorders (415.0, 415.1, 416.x, 417.0, 417.8, 417.9), uncomplicated (401.x) and complicated (402.x - 405.x) hypertension, chronic pulmonary disease (416.8, 416.9, 490.x - 505.x, 506.4, 508.1, 508.8), uncomplicated (250.0 - 250.3) and complicated (250.4 - 250.9) diabetes mellitus, renal failure (403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 585.x, 586.x, 588.0, V42.0, V45.1, V56.x), coagulopathy (286.x, 287.1, 287.3 - 287.5), alcohol abuse (265.2, 291.1 - 291.3, 291.5 - 291.9, 303.0, 303.9, 305.0, 357.5, 425.5, 535.3, 571.0 - 571.3, 980.x, V11.3), and drug abuse (292.x, 304.x, 305.2 - 305.9, V65.42).

Myocardial Infarction and Outcomes

We defined AMI as a diagnosis of acute ST-segment elevation myocardial infarction (STEMI, 410.0-410.02, 410.1-410.12, 410.2-410.22, 410.3-410.32, 410.4-410.42, 410.5-410.52, 410.6-410.62, 410.8-410.82, 410.9-410.92) or acute non-ST-segment elevation myocardial infarction (NSTEMI, 410.7-410.72). Our outcome of primary interest was poor functional status at discharge, which we defined using the NIS severity outcome measure (NIS-SOM).[14] The NIS-SOM is a composite outcome score in which poor functional status is defined as the presence of any of the following: (1) in-hospital mortality, (2) discharge to a nursing facility, extended care facility or hospice, (3) placement of a tracheostomy tube (31.1, 31.2.31.21, 31.29), and/or (4) placement of a

gastrostomy tube (43.1, 43.11, 43.19, 44.32, 44.38, 44.39). The NIS-SOM has been validated to have a strong correlation with a modified Ranking scale greater than 3. Outcomes of secondary interest were in-hospital mortality, length of stay, and total monetary charges adjusted for inflation to December of 2014 using Consumer Price Indexes for the included years obtained from the US Bureau of Labor Statistics.[16]

Statistical Analysis

We used R version 3.6.1 to perform our statistical analysis (R Foundation for Statistical Computing, Vienna, Austria).[17] We also used the survey, comorbidity, and metafor R packages.[18–20] After assessing for patient inclusion and exclusion criteria, we estimated yearly summary statistics for the population's demographics, cardiovascular risk factors, SAH characteristics, AMI characteristics, and outcomes, accounting for the complex survey design of the NIS. We then pooled these yearly estimates using mixed effects models to obtain summary statistics for the entire population across years. Using the summary statistics of the entire population we performed chi-square and t-tests to evaluate associations between patient characteristics and AMI. Using these statistical tests, we selected patient demographics, SAH characteristics, and cardiovascular risk factors associated with AMI with a p-value <0.05 to use as confounders for our inverse probability weighted analysis. To test the association between AMI and our outcomes of interest, we performed yearly analyses calculating stabilized inverse probability weights using the previously mentioned confounders. We obtained the product of these stabilized inverse probability weights and the original trend weights and used these products as new weights to perform an adjusted survey analysis.[21,22] Finally, yearly effect estimates were pooled using mixed effects models.

RESULTS

Incidence of Acute Myocardial Infarction after Subarachnoid Hemorrhage

139,732 individuals were identified in this study with aneurysmal SAH, of which 4993 (3.6%) developed AMI (Table 1). Of the patients with AMI, 30% had STEMI. The incidence of AMI after aSAH was highest in 2008 (4.3%, 95%CI: 3.5% – 5.4%), but overall, the incidence of AMI after aSAH remained stable across years with no evident temporal trends observed over time (Figure 1).

Characteristics of Patients with AMI after aSAH

When compared to non-AMI patients, patients who had AMI after aSAH were older (61.1 years vs. 54.3 years) and more likely to be female (74% vs. 68%) (Table 1). Patients with AMI were also more likely to have a history of congestive heart failure, cardiac arrhythmia, valvular disease, chronic pulmonary disease, uncomplicated diabetes, or coagulopathy, but less likely to have pulmonary circulation disorders, uncomplicated and complicated hypertension, complicated diabetes, renal failure, alcohol abuse and drug abuse (Table 1). Patients with AMI after aSAH were more likely to have a high grade aSAH (69% vs. 38%), more commonly treated with endovascular coiling (62% vs. 52%) and were more commonly insured by Medicare or Medicaid (52% vs. 39%) (Table 1). Poor functional status (83% vs. 55%) and in-hospital mortality (28% vs. 13%) were more common in patients with AMI after aSAH (Table 1). Similarly, hospitalization was longer (23 days vs. 18 days) and more costly ($350,793 USD vs. $260,422 USD) (Table 1).

Association between AMI and Outcomes

After adjusting for age, sex, poor SAH grade, aneurysm treatment modality, and cardiovascular risk factors, AMI after aSAH was associated with higher odds of poor functional status at discharge (Odds ratio (OR): 2.27, 95% CI: 2.1 – 2.4, p<0.001) and in-hospital mortality (OR: 1.8, 95% CI: 1.7 – 19, p<0.001) (Figures 2 - 3). AMI after aSAH was also associated with a longer (mean difference (MD): 3.84 days, 95% CI: 2.9 – 4.8, p<0.001) and more costly (MD: $70,774 USD, 95% CI: $56,266 – $85,282, p<0.001) hospitalization (Figures 4 - 5). STEMI was also associated with higher odds of poor functional status at discharge (OR: 3.2, 95% CI: 2.8 – 3.7, p<0.001) and in-hospital mortality (OR: 2.2, 95% CI: 1.9 – 2.5, p<0.001), and a longer (MD: 5.1 days, 95% CI: 3.4 – 6.8, p<0.001) and more costly (MD: $46,621 USD, 95% CI: $23,536 – $75,706, p<0.001) hospitalization when compared to non-AMI patients (Figures 2 - 5). Similarly, when compared to non-AMI patients, NSTEMI was associated with higher odds of poor functional status at discharge (OR: 2, 95% CI: 1.9 – 2.2, p<0.001) and in-hospital mortality (OR: 1.65, 95% CI: 1.5 – 1.8, p<0.001), and a longer (MD: 3.3 days, 95% CI: 2.2. – 4.4, p<0.001) and more costly (MD: $77,204 USD, 95% CI: $60,062 – $94,346, p<0.001) hospitalization (Figures 2 - 5).

DISCUSSION

In this study, we found that the incidence of AMI after aSAH is 3.6%, with NSTEMI being the most common type of AMI occurring after aSAH (70% vs. 30% for NSTEMI vs. STEMI, respectively). Patients developing AMI after aSAH were older, more commonly female, had a distinct profile of cardiovascular risk factors, more likely to have a poor SAH grade, and more commonly insured by Medicare or Medicaid. Finally, patients with AMI after aSAH had higher

odds of poor functional status at discharge and in-hospital mortality, and a longer and more costly hospital stay after adjusting for baseline characteristics.

Death or disability are common after aSAH, occurring in approximately two-thirds of all aSAH patients.[23] Due to advances in endovascular treatment and management of vasospasm, aSA. H mortality has dropped sizably in recent years.[23,24] These reductions in aSAH mortality – however – have come at the expense of increased rates of disability after SAH, with poor cognitive and functional outcomes being common after aSAH.[25] In addition to delayed ischemic neurological deficits, medical complications are important drivers of disability beyond the initial effects of an aSAH.[26] The role that medical complications have in causing patient disability make their study essential for continued improvement of outcomes after aSAH.

Cardiac complications of aSAH include sudden death, transient left ventricular dysfunction, and AMI.[27–29] One out of every four patients with aSAH dies before reaching hospital admission.[27] The exact mechanisms of aSAH-related sudden death are unknown, but risk factors for aSAH-related sudden death are similar to those of sudden cardiac death suggesting altered cardiovascular function is a likely culprit.[27] Transient left ventricular dysfunction and AMI after aSAH lie within the spectrum of what is commonly known as neurogenic stress cardiomyopathy.[30] Neurogenic stress cardiomyopathy is myocardial injury or dysfunction that is directly caused by neurological activity.[31] Once regarded as a rare complication, neurogenic stress cardiomyopathy is now known to be common after aSAH, with myocardial injury occurring in 40% of all subarachnoid hemorrhage cases.[2] Most cases of neurogenic stress cardiomyopathy manifest as transient left

ventricular dysfunction, which occurs in 30% of aSAH cases and is associated with poor functional outcome.[28,32,33]

AMI is the rarest and least studied cardiac complication of aSAH. In a previous study of the NIS, the incidence of AMI after aSAH was estimated at 0.28% by Kim et al.[34] The incidence of AMI after acute ischemic stroke, however, is higher (1.6%).[34,35] Given that the incidence of myocardial injury is higher in patients with subarachnoid hemorrhage than in patients with ischemic stroke, we expected the incidence of AMI after aSAH to be higher.[2] In our analysis, we found that the incidence of AMI after aSAH is 3.6%.[34] Analysis of the NIS requires careful accounting for the complex survey design imposed on the data and the use of appropriate methods for combining data across multiple years.[11,36] By performing independent yearly analyses we not only assessed for trends in the incidence of AMI after aSAH across time, we also observed the independent yearly estimates before pooling them across years using mixed effects models. Additionally, by using the newly available HCUP trend weights, we produced a national-level estimate of AMI after aSAH. This approach allowed us to obtain a more precise estimate of the incidence of AMI after aSAH.

Patient characteristics associated with AMI after aSAH included increased age, female gender, poor subarachnoid hemorrhage grade, and diverse cardiovascular risk factors. Female gender has been consistently reported as a risk factor for neurogenic stress cardiomyopathy.[30] Differences in sensitivity to the effect of adrenergic agonists across genders have been reported and may explain the higher incidence of cardiac complications of aSAH observed in women.[37] Poor aSAH grade was also associated with AMI after aSAH. Indeed, troponin levels after aSAH directly correlate with aSAH grade and have been proposed as an objective biomarker of SAH severity for outcome

prediction.[38] Interestingly, various cardiovascular risk factors appeared to be protective of AMI after aSAH, namely hypertension, pulmonary circulation disorders and renal failure. These conditions are commonly managed with adrenergic receptor blockers or antagonists of the renin angiotensin aldosterone pathway, and pre-treatment with either one of these drug classes has been associated with improved functional outcomes after stroke.[39,40] In line with our current findings, we previously reported an inverse association between hypertension and myocardial injury after aSAH.[41]

AMI after aSAH was associated with poor functional status at discharge and in-hospital mortality, and a longer and more costly hospital stay. Managing AMI in the setting of aSAH can be difficult as treatment strategies for both conditions are often at odds with each other and must be weighed carefully. Differentiation of type 1 vs. type 2 AMI requires coronary angiography which is relatively contraindicated in patients with SAH.[3] In these patients, cardiac computed tomography angiography may be a useful alternative for diagnosing AMI.[3] Once a more precise diagnosis is obtained, the risks and benefits of percutaneous coronary intervention can be weighted in patients with type 1 AMI. In patients with type 2 AMI, on the other hand, strategies aimed at optimizing myocardial supply and demand may be of important value as the management of SAH often involves inotropes which may worsen cardiac injury.[42]

LIMITATIONS

Limitations of our study include those inherent to the nature of our question and those inherent to the design of the NIS. Given that our question of interest is to evaluate the effect of AMI on

outcomes after SAH, we were unable to obtain data on some of the confounders that are known to be associated with outcomes after SAH (e.g. aneurysm diameter). Therefore, although we did adjust for some of the confounders for the association between AMI and outcomes after SAH, we did not adjust for all of the known confounders. Our estimates remain confounded and should not be interpreted as causal. Due to the design of the NIS, specifically the lack of admission flags, it is not possible to know with certainty whether a certain diagnosis was present or not before the patient's admission. We worked under the assumption that diagnosis codes reflecting acute conditions were adequately coded, but miscoding is possible and should be considered when interpreting our results. Similarly, because ICD-9 codes did not incorporate the new universal definition of AMI, we were not able to evaluate the incidence of type 1 vs. type 2 AMI. These distinctions are available in the ICD-10, and may be estimated once data on a greater number of years using the ICD-10 system becomes available.

CONCLUSION

The incidence of AMI after aSAH is 3.6%, with NSTEMI as the most common type of AMI occurring after aSAH. Patients developing AMI after aSAH were older, more commonly female, had a distinct profile of cardiovascular risk factors, and more likely to have a poor SAH grade. Patients with AMI after aSAH had higher odds of poor functional status at discharge and in-hospital mortality, and a longer and more costly hospital stay after adjusting for baseline characteristics.

REFERENCES

1. Morris NA, Chatterjee A, Adejumo OL, et al. The Risk of Takotsubo Cardiomyopathy in Acute Neurological Disease. *Neurocrit Care*. 2019;30(1):171-176. doi:10.1007/s12028-018-0591-z

2. Alkhachroum AM, Miller B, Chami T, Tatsuoka C, Sila C. A troponin study on patients with ischemic stroke, intracerebral hemorrhage and subarachnoid hemorrhage: Type II myocardial infarction is significantly associated with stroke severity, discharge disposition and mortality. *J Clin Neurosci*. 2019;64:83-88. doi:10.1016/j.jocn.2019.04.005

3. Ghadri J-R, Wittstein IS, Prasad A, et al. International Expert Consensus Document on Takotsubo Syndrome (Part II): Diagnostic Workup, Outcome, and Management. *Eur Heart J*. 2018;39(22):2047-2062. doi:10.1093/eurheartj/ehy077

4. Fujita K, Fukuhara T, Munemasa M, Numba Y, Kuyama H. Ampulla cardiomyopathy associated with aneurysmal subarachnoid hemorrhage: report of 6 patients. *Surg Neurol*. 2007;68(5):556-561. doi:10.1016/j.surneu.2006.11.041

5. Ridwan S, Kristof R. Cardiac Arrest in Patients with Poor-Grade Aneurysmal Subarachnoid Hemorrhage: A Single-Center Experience. *J Neurol Surg Part Cent Eur Neurosurg*. 2019;80(06):409-412. doi:10.1055/s-0039-1685506

6. Kimura T, Kamide T, Onodera K, et al. Clinical Features of Neurogenic Pulmonary Edema in Patients with Subarachnoid Hemorrhage. *World Neurosurg*. December 2019:S187887501933089X. doi:10.1016/j.wneu.2019.12.060

7. Cho S-M, Geocadin RG, Caturegli G, et al. Understanding Characteristics of Acute Brain Injury in Adult Extracorporeal Membrane Oxygenation: An Autopsy Study. *Crit Care Med*. February 2020:1. doi:10.1097/CCM.0000000000004289

8. DeFilippis AP, Chapman AR, Mills NL, et al. Assessment and Treatment of Patients With Type 2 Myocardial Infarction and Acute Nonischemic Myocardial Injury. *Circulation*. 2019;140(20):1661-1678. doi:10.1161/CIRCULATIONAHA.119.040631

9. HCUP Overview Course - Accessible Version. https://www.hcup-us.ahrq.gov/HCUP_Overview/HCUP_Overview/index508_2019.jsp. Accessed February 3, 2020.

10. Producing National HCUP Estimates - Accessible Version. https://www.hcup-us.ahrq.gov/tech_assist/nationalestimates/508_course/508course_2018.jsp#redesign. Accessed February 3, 2020.

11. NIS Trend Weights. https://www.hcup-us.ahrq.gov/db/nation/nis/trendwghts.jsp. Accessed February 3, 2020.

12. Release of the 2015 National Inpatient Sample (NIS) (November 2017). https://www.hcup-us.ahrq.gov/news/announcements/nis_111517.jsp. Accessed February 3, 2020.

13. Elixhauser A, Heslin K, Owens P. Healthcare Cost and Utilization Project (HCUP) Recommendations for Reporting Trends Using ICD-9-CM and ICD-10-CM/PCS Data. https://www.hcup-us.ahrq.gov/datainnovations/HCUP_RecomForReportingTrends_070517.pdf. Accessed February 3, 2020.

14. Washington CW, Derdeyn CP, Dacey RG, Dhar R, Zipfel GJ. Analysis of subarachnoid hemorrhage using the Nationwide Inpatient Sample: the NIS-SAH Severity Score and Outcome Measure. *J Neurosurg*. 2014;121(2):482-489. doi:10.3171/2014.4.JNS131100

15. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. *Med Care*. 1998;36(1):8-27. doi:10.1097/00005650-199801000-00004

16. CPI Home : U.S. Bureau of Labor Statistics. https://www.bls.gov/cpi/. Accessed February 28, 2020.

17. R Core Team. *R: A Language and Environment for Statistical Computing*. Viena, Austria: R Foundation for Statistical Computing; 2019. https://www.R-project.org/.

18. Gasparini. comorbidity: An R package for computing comorbidity scores. *J Open Source Softw*. 3(23):648. doi:https://doi.org/10.21105/joss.00648

19. Lumley T. Analysis of Complex Survey Samples. *J Stat Softw*. 2004;9(1):1-19.

20. Viechtbauer W. Conducting meta-analyses in R with the metafor package. *J Stat Softw*. 36(3):1-48.

21. Rubin DB. *Matched Sampling for Causal Effects*. Cambridge: Cambridge University Press; 2006. doi:10.1017/CBO9780511810725

22. DuGoff EH, Schuler M, Stuart EA. Generalizing Observational Study Results: Applying Propensity Score Methods to Complex Surveys. *Health Serv Res*. 2014;49(1):284-303. doi:10.1111/1475-6773.12090

23. Lovelock CE, Rinkel GJE, Rothwell PM. Time trends in outcome of subarachnoid hemorrhage: Population-based study and systematic review. *Neurology*. 2010;74(19):1494-1501. doi:10.1212/WNL.0b013e3181dd42b3

24. Lantigua H, Ortega-Gutierrez S, Schmidt JM, et al. Subarachnoid hemorrhage: who dies, and why? *Crit Care*. 2015;19(1):309. doi:10.1186/s13054-015-1036-0

25. Al-Khindi T, Macdonald RL, Schweizer TA. Cognitive and Functional Outcome After Aneurysmal Subarachnoid Hemorrhage. *Stroke*. 2010;41(8). doi:10.1161/STROKEAHA.110.581975

26. Kassel, NF, Torner, JC, Jane, JA, Haley, EC Jr, Adams HP. The International Cooperative Study on the Timing of Aneurysm Surgery. *J Neurosurg*. 1990;73(1):37-47.

27. Lindbohm JV, Kaprio J, Jousilahti P, Salomaa V, Korja M. Risk Factors of Sudden Death From Subarachnoid Hemorrhage. *Stroke*. 2017;48(9):2399-2404. doi:10.1161/STROKEAHA.117.018118

28. van der Bilt I, Hasan D, van den Brink R, et al. Cardiac dysfunction after aneurysmal subarachnoid hemorrhage: Relationship with outcome. *Neurology*. 2014;82(4):351-358. doi:10.1212/WNL.0000000000000057

29. van der Velden LBJ, Otterspoor LC, Kool LJS, Biessels GJ, Verheugt FWA. Acute myocardial infarction complicating subarachnoid haemorrhage. *Neth Heart J*. 2009;17(7):284-287. doi:10.1007/BF03086267

30. Bybee KA, Prasad A. Stress-Related Cardiomyopathy Syndromes. *Circulation*. 2008;118(4):397-409. doi:10.1161/CIRCULATIONAHA.106.677625

31. Samuels MA. The Brain–Heart Connection. *Circulation*. 2007;116(1):77-84. doi:10.1161/CIRCULATIONAHA.106.678995

32. Kilbourn KJ, Levy S, Staff I, Kureshi I, McCullough L. Clinical characteristics and outcomes of neurogenic stress cadiomyopathy in aneurysmal subarachnoid hemorrhage. *Clin Neurol Neurosurg*. 2013;115(7):909-914. doi:10.1016/j.clineuro.2012.09.006

33. Banki N, Kopelnik A, Tung P, et al. Prospective analysis of prevalence, distribution, and rate of recovery of left ventricular systolic dysfunction in patients with subarachnoid hemorrhage. *J Neurosurg*. 2006;105(1):15-20. doi:10.3171/jns.2006.105.1.15

34. Kim YW, Neal D, Hoh BL. Risk Factors, Incidence, and Effect of Cardiac Failure and Myocardial Infarction in Aneurysmal Subarachnoid Hemorrhage Patients. *Neurosurgery*. 2013;73(3):450-457. doi:10.1227/NEU.0000000000000001

35. Alqahtani F, Aljohani S, Tarabishy A, Busu T, Adcock A, Alkhouli M. Incidence and Outcomes of Myocardial Infarction in Patients Admitted With Acute Ischemic Stroke. *Stroke*. 2017;48(11):2931-2938. doi:10.1161/STROKEAHA.117.018408

36. HCUP Using Multiple Years of Data - Accessible Version. https://www.hcup-us.ahrq.gov/tech_assist/trends/508/508course_2015.jsp. Accessed March 2, 2020.

37. Kneale BJ, Chowienczyk PJ, Brett SE, Coltart DJ, Ritter JM. Gender differences in sensitivity to adrenergic agonists of forearm resistance vasculature. *J Am Coll Cardiol*. 2000;36(4):1233-1238. doi:10.1016/S0735-1097(00)00849-4

38. Guette P, Launey Y, Arnouat M, et al. Prognostic value of high-sensitivity troponin T in aneurysmal subarachnoid hemorrhage: a prospective observational study. *Brain Inj*. 2019;33(10):1372-1378. doi:10.1080/02699052.2019.1641742

39. Neil-Dwyert G, Walter P, Cruickshank JM, PharmaceuticalsDivision Ici. B-Blockade Benefits Patients Following a Subarachnoid Haemorrhage. :5.

40. Hassan Y, Al-Jabi SW, Aziz NA, Looi I, Zyoud SH. Effect of Prestroke Use of Angiotensin-Converting Enzyme Inhibitors Alone Versus Combination With Antiplatelets and Statin on Ischemic Stroke Outcome: *Clin Neuropharmacol*. 2011;34(6):234-240. doi:10.1097/WNF.0b013e3182348abe

41. Malik AN, Gross BA, Rosalind Lai PM, Moses ZB, Du R. Neurogenic Stress Cardiomyopathy After Aneurysmal Subarachnoid Hemorrhage. *World Neurosurg*. 2015;83(6):880-885. doi:10.1016/j.wneu.2015.01.013

42. Participants in the International Multi-disciplinary Consensus Conference on the Critical Care Management of Subarachnoid Hemorrhage, Treggiari MM. Hemodynamic Management of Subarachnoid Hemorrhage. *Neurocrit Care*. 2011;15(2):329-335. doi:10.1007/s12028-011-9589-5

TABLES AND FIGURES

Table 1. Population characteristics.

	Total	Acute Myocardial Infarction		
		No	*Yes*	*p*
	N (%)	N (%)	N (%)	
Number of patients	139,732 (100)	134,739 (96.4)	4,993 (3.6)	
Demographics and CV Risk Factors				
Age, mean ± SD	54.6 ± 0.2	54.3 ± 0.2	61.1 ± 0.5	<0.001
Female	95,732 (68.5)	92,043 (68.3)	3,670 (73.5)	<0.001
CHF	8,666 (6.2)	7,111 (5.3)	1,546 (31.0)	<0.001
Arrhythmia	21,564 (15.4)	20,246 (15.0)	1,347 (27.0)	<0.001
Valvular disease	3,823 (2.7)	3,536 (2.6)	316 (6.3)	<0.001
Pulmonary circulation disorders	3,047 (2.2)	2,793 (2.1)	45 (0.9)	<0.001
Uncomplicated hypertension	76,152 (54.5)	73,610 (54.6)	2,556 (51.2)	<0.001
Complicated hypertension	3,524 (2.5)	3,346 (2.5)	28 (0.6)	<0.001
Chronic pulmonary disease	18,680 (13.4)	17,775 (13.2)	920 (18.4)	<0.001
Uncomplicated diabetes	12,660 (9.1)	12,047 (8.9)	611 (12.2)	<0.001
Complicated diabetes	1,118 (0.8)	1,088 (0.8)	0 (0)	<0.001
Renal failure	3,128 (2.2)	2,937 (2.2)	6 (0.1)	<0.001
Coagulopathy	6,783 (4.9)	6,280 (4.7)	474 (9.5)	<0.001
Alcohol abuse	8,213 (5.9)	7,991 (5.9)	35 (0.7)	<0.001

Drug abuse	7,672 (5.5)	7,485 (5.6)	208 (4.2)	<0.001
SAH Characteristics				
Poor grade SAH	54,128 (38.7)	50,676 (37.6)	3,447 (69)	<0.001
Clip	68,561 (49.1)	66,639 (49.5)	1,961 (39.3)	<0.001
Coil	72,678 (52)	69,572 (51.6)	3,081 (61.7)	<0.001
Hospital location/teaching status				0.54
Rural	1,523 (1.1)	1,469 (1.1)	58 (1.1)	
Urban non-teaching	17,143 (12.3)	16,514 (12.3)	635 (12.7)	
Urban teaching	121,066 (86.6)	116,757 (86.7)	4,300 (86.1)	
Primary payer				<0.001
Private insurance	63,549 (45.5)	61,633 (45.7)	2,057 (41.2)	
Medicare/Medicaid	54,898 (39.3)	52,341 (38.8)	2,579 (51.7)	
Self-pay	14,167 (10.1)	13,837 (10.3)	352 (7)	
Other	7,118 (5.1)	6,927 (5.1)	5 (0.1)	
AMI Characteristics				
STEMI	1,548 (1.1)	0 (0)	1,508 (30)	
NSTEMI	3,549 (2.5)	0 (0)	3,507 (70)	
*Outcomes**				
Poor functional status at discharge	77,718 (55.6)	73,590 (54.6)	4,123 (82.6)	<0.001
Inpatient mortality	18,151 (13)	16,784 (12.5)	1,374 (27.5)	<0.001
Length of stay, mean ± SD	18.6 ± 0.1	18.4 ± 0.1	22.5 ± 0.6	<0.001
Total charges, mean ± SD	$263,983.3 ± $17,347.7	$260,422.4 ± $17,068.3	$350,792.9 ± $25,145.5	<0.001

Abbreviations: N: number, CV: cardiovascular, SD: standard deviation, CHF: congestive heart failure, SAH: subarachnoid hemorrhage, AMI: acute myocardial infarction, STEMI: ST-segment elevation myocardial infarction, NSTEMI: non-ST-segment elevation myocardial infarction.

* Unadjusted analyses.

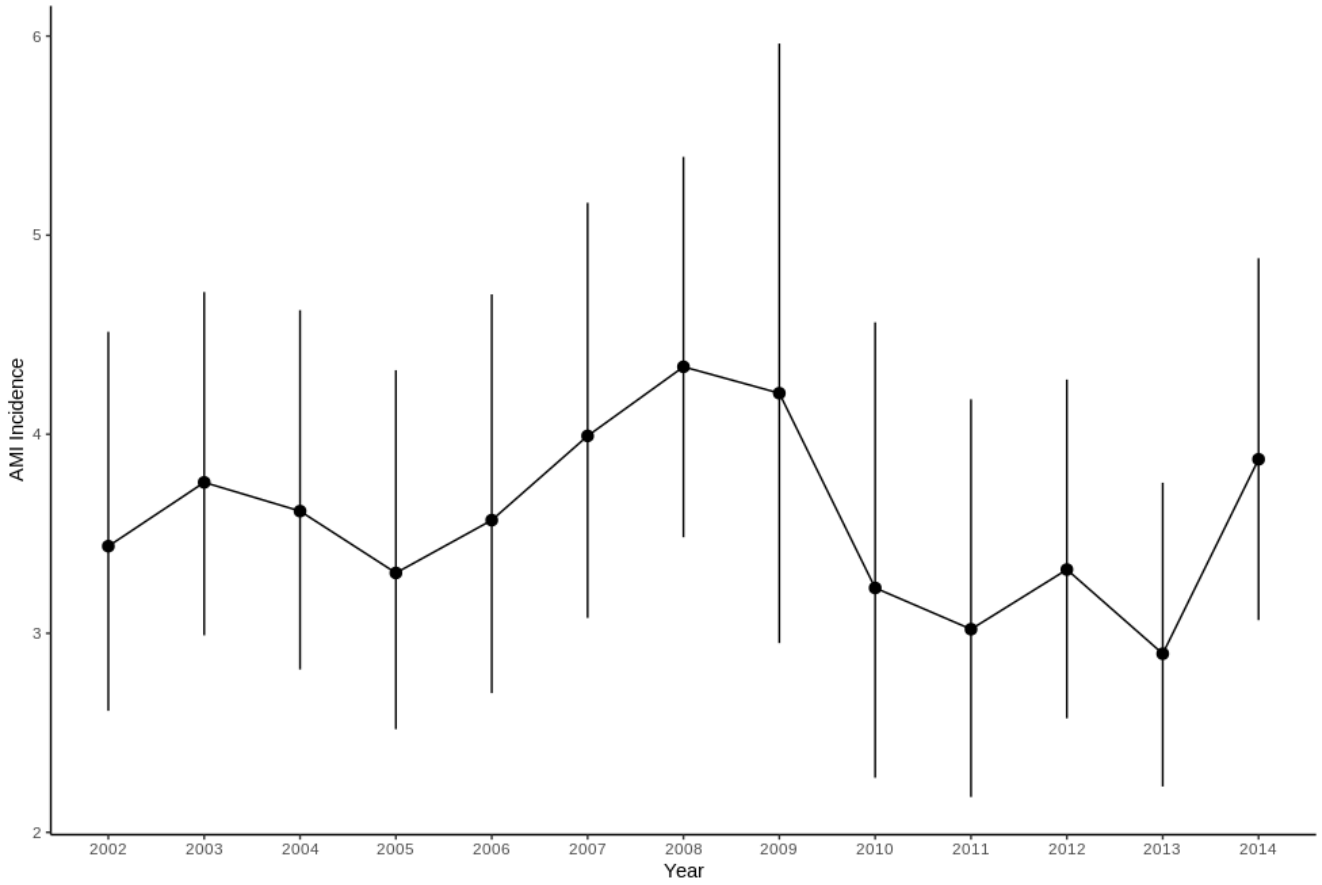


Figure 1. Incidence trends of AMI after aSAH.

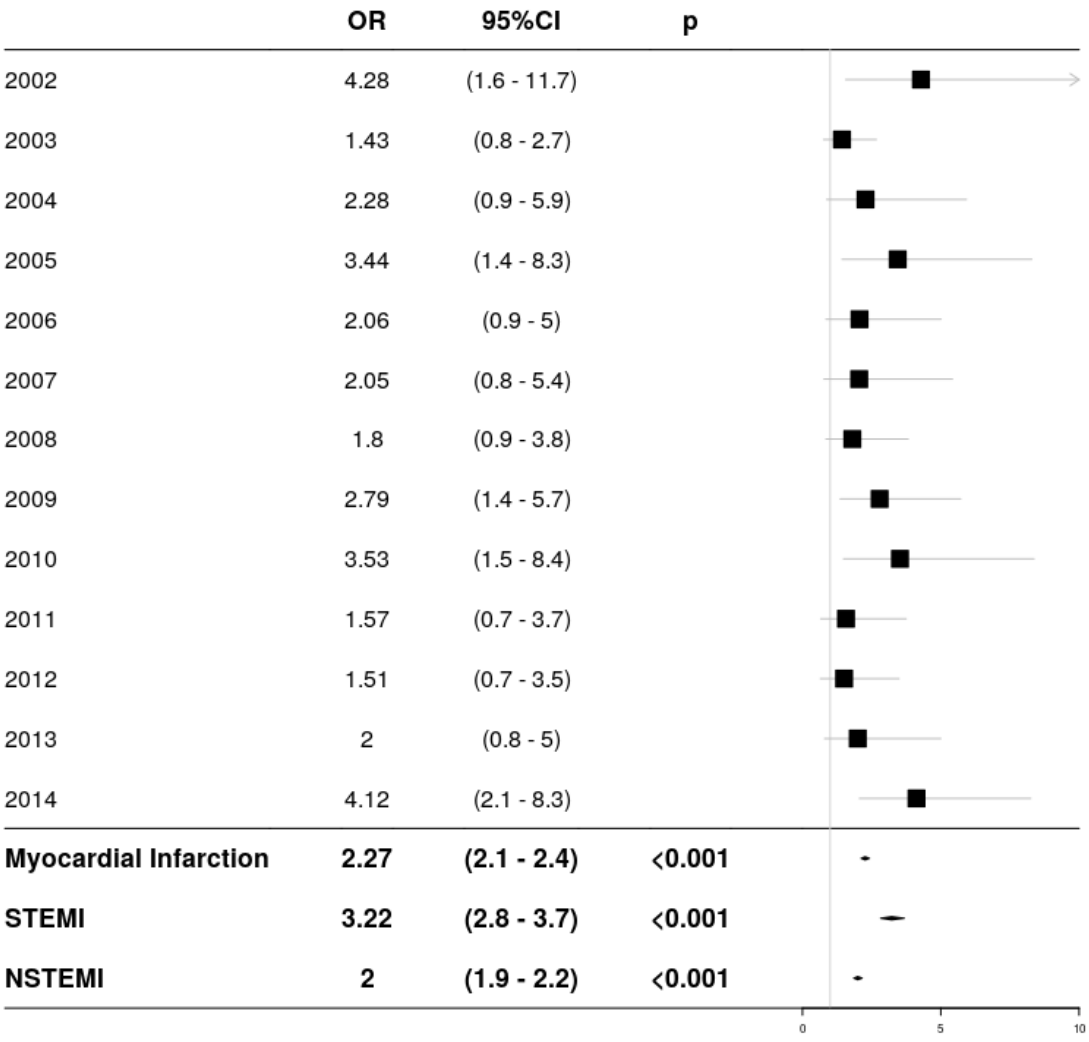


Figure 2. Adjusted association between AMI after aSAH and poor functional outcome at hospital discharge.

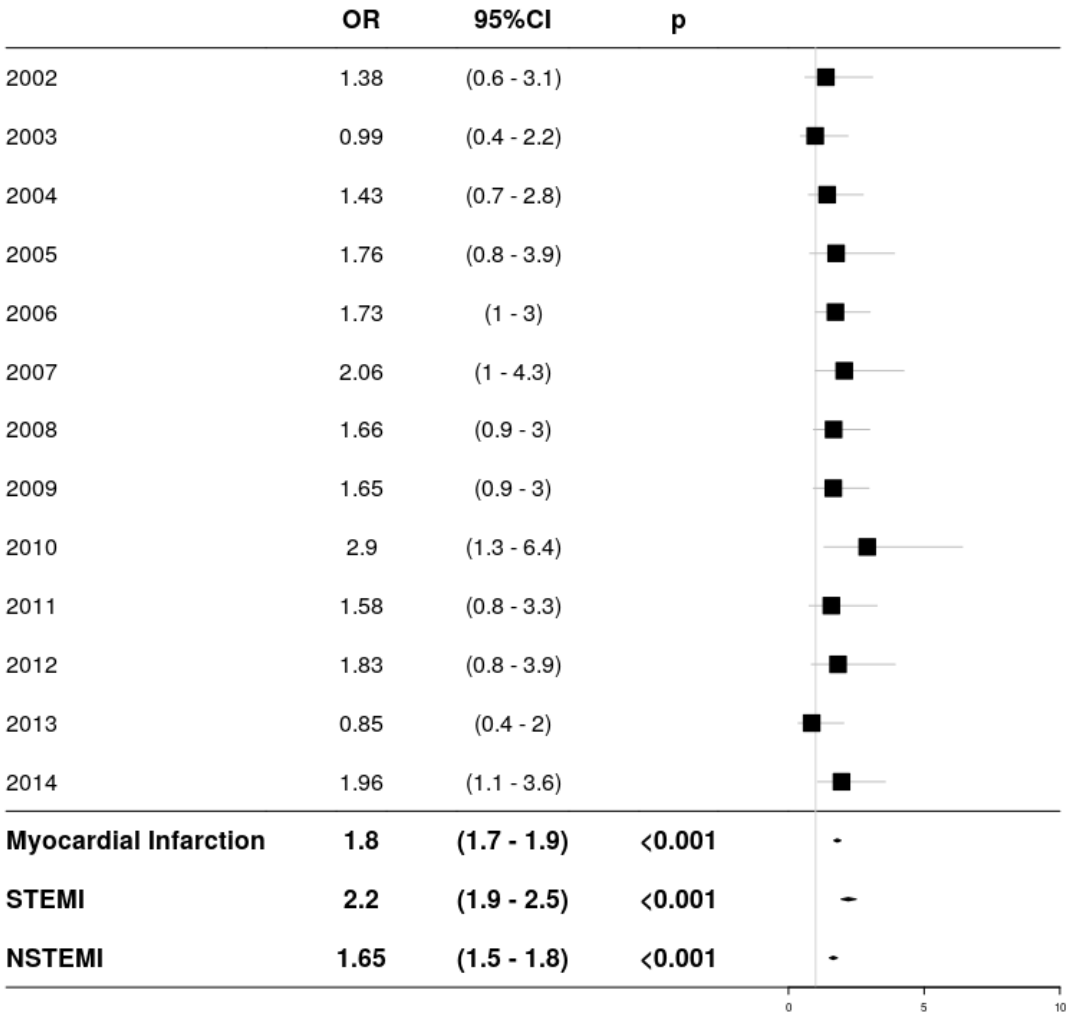


Figure 3. Adjusted association between AMI after aSAH and in-hospital mortality.

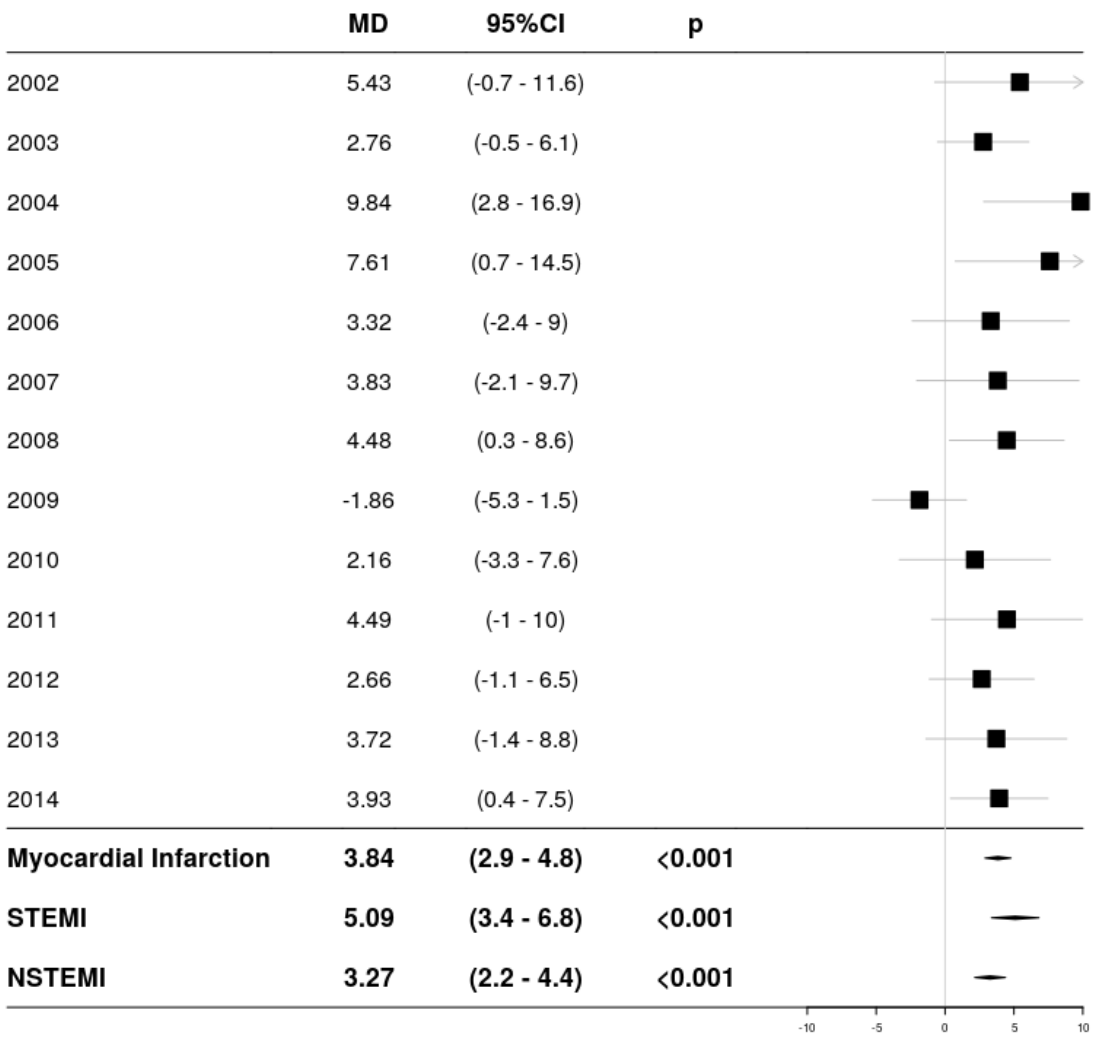


Figure 4. Adjusted association between AMI after aSAH and length of stay.

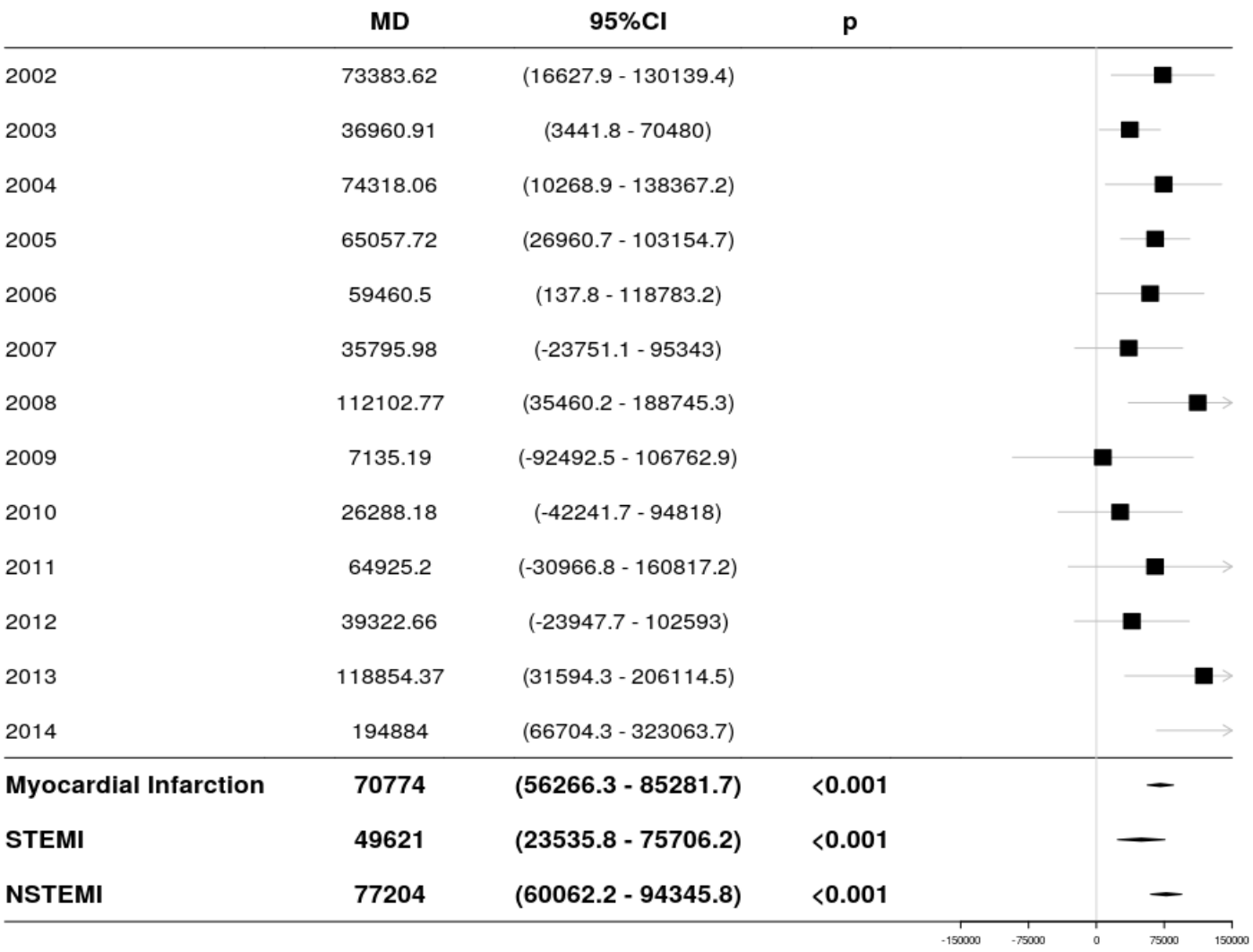


Figure 5. Adjusted association between AMI after aSAH and hospitalization total charges.

SUPPLEMENTARY MATERIALS: Incidence and Outcomes of Acute Myocardial Infarction after Aneurysmal Subarachnoid Hemorrhage.

Christian D. Cerecedo-Lopez, MD[1]; Issac Ng[1], BSc; Hillary B. Nguyen, BA[1]; Pui Man Rosalind Lai[1], MD; William B. Gormley, MD, MPH, MBA[1], Nirav Patel, MD, MA[1], Kai U. Frerichs, MD[1], M. Ali Aziz-Sultan, MD, MBA[1], Rose Du, MD, PhD[1,*].

Table S1. Multivariate Regression for Acute Myocardial Infarction and Functional Status at Discharge.

	OR	95% CI	p
Myocardial Infarction	1.77	(1.63 - 1.93)	<0.01
Age	1.05	(1.05 - 1.05)	<0.01
Female	0.97	(0.94 - 1)	0.03
Poor grade on admission	8.55	(8.31 - 8.8)	<0.01
Aneurysm Clipping	1.6	(1.49 - 1.72)	<0.01
Aneurysm Coiling	1.12	(1.04 - 1.21)	<0.01
CHF	1.45	(1.36 - 1.54)	<0.01
Arrythmia	1.47	(1.42 - 1.52)	<0.01
Valvular disease	1.07	(0.99 - 1.16)	0.1
Pulmonary Circulation Disorder	2.1	(1.9 - 2.32)	<0.01
Uncomplicated hypertension	0.89	(0.87 - 0.92)	<0.01
Complicated hypertension	0.99	(0.86 - 1.13)	0.87
Chronic Pulmonary Disease	1	(0.96 - 1.03)	0.82
Uncomplicated diabetes	1.28	(1.22 - 1.34)	<0.01
Complicated diabetes	1.85	(1.58 - 2.16)	<0.01
Renal failure	1.35	(1.17 - 1.55)	<0.01
Coagulopathy	1.71	(1.6 - 1.82)	<0.01
Alcohol abuse	1.14	(1.08 - 1.2)	<0.01
Drug abuse	0.95	(0.89 - 1)	0.05

Abbreviations: OR = odds ratio, CI = confidence interval, CHF = congestive heart failure.

Table S2. Multivariate Regression for Acute Myocardial Infarction and In-Hospital Mortality.

	OR	95% CI	p
Myocardial Infarction	1.07	(1.05 – 1.09)	<0.01
Age	1	(1 - 1)	<0.01
Female	1	(0.99 - 1.01)	0.96
Poor grade on admission	1.24	(1.23 - 1.25)	<0.01
Aneurysm Clipping	0.99	(0.97 - 1.02)	0.6
Aneurysm Coiling	1	(0.98 - 1.02)	0.69
CHF	0.99	(0.97 - 1)	0.09
Arrythmia	1.01	(1 - 1.02)	0.01
Valvular disease	0.99	(0.97 - 1.01)	0.34
Pulmonary Circulation Disorder	0.96	(0.94 - 0.99)	<0.01
Uncomplicated hypertension	0.99	(0.98 - 0.99)	<0.01
Complicated hypertension	1	(0.96 - 1.04)	0.98
Chronic Pulmonary Disease	0.99	(0.98 - 1)	0.11
Uncomplicated diabetes	0.99	(0.98 - 1.01)	0.29
Complicated diabetes	0.97	(0.93 - 1.01)	0.11
Renal failure	1.05	(1.01 - 1.09)	0.01
Coagulopathy	1.05	(1.03 - 1.07)	<0.01
Alcohol abuse	0.98	(0.97 - 1)	0.04
Drug abuse	0.99	(0.98 - 1.01)	0.31

Abbreviations: OR = odds ratio, CI = confidence interval, CHF = congestive heart failure.

Table S3. Multivariate Regression for Acute Myocardial Infarction and Length of Hospital Stay.

	MD	95% CI	p
Myocardial Infarction	1.44	(0.54 ; 2.34)	<0.01
Age	0.01	(-0.01 ; 0.02)	0.35
Female	-0.44	(-0.8 ; -0.09)	0.02
Poor grade on admission	6.35	(6.01 ; 6.7)	<0.01
Aneurysm Clipping	5.09	(4.15 ; 6.02)	<0.01
Aneurysm Coiling	3.09	(2.15 ; 4.02)	<0.01
CHF	2.44	(1.73 ; 3.15)	<0.01
Arrythmia	0.87	(0.42 ; 1.32)	<0.01
Valvular disease	-0.43	(-1.43 ; 0.57)	0.4
Pulmonary Circulation Disorder	9.43	(8.32 ; 10.53)	<0.01
Uncomplicated hypertension	-1.34	(-1.68 ; -0.99)	<0.01
Complicated hypertension	0.02	(-1.62 ; 1.65)	0.98
Chronic Pulmonary Disease	-1.05	(-1.53 ; -0.56)	<0.01
Uncomplicated diabetes	0.42	(-0.15 ; 0.99)	0.15
Complicated diabetes	3.86	(2.05 ; 5.67)	<0.01
Renal failure	1.06	(-0.63 ; 2.75)	0.22
Coagulopathy	3.63	(2.88 ; 4.38)	<0.01
Alcohol abuse	1.1	(0.39 ; 1.81)	<0.01
Drug abuse	0.58	(-0.15 ; 1.3)	0.12

Abbreviations: MD = mean difference, CI = confidence interval, CHF = congestive heart failure.

Table S4. Multivariate Regression for Acute Myocardial Infarction and Total Hospitalization Charges.

	MD	95% CI	p
Myocardial Infarction	$43,519.5	($30,004.3 ; $57,034.8)	<0.01
Age	-$400.5	(-$592.1 ; -$208.9)	<0.01
Female	-$3,100	(-$8,462.3 ; $2,262.3)	0.26
Poor grade on admission	$118,714.6	($113,568.7 ; $123,860.5)	<0.01
Aneurysm Clipping	$117,748.5	($103,702.2 ; $131,794.8)	<0.01
Aneurysm Coiling	$141,247.5	($127,195 ; $155,300.1)	<0.01
CHF	$37,352.8	($26,718.1 ; $47,987.4)	<0.01
Arrythmia	$29,680.9	($22,894.7 ; $36,467.2)	<0.01
Valvular disease	$7,472.7	(-$7,555.1 ; $22,500.4)	0.33
Pulmonary Circulation Disorder	$122,175.5	($105,580.6 ; $138,770.5)	<0.01
Uncomplicated hypertension	$5,080.5	(-$70.4 ; $10,231.3)	0.05
Complicated hypertension	$28,421.3	($3,897.9 ; $52,944.6)	0.02
Chronic Pulmonary Disease	-$18,836.3	(-$26,173.2 ; -$11,499.4)	<0.01
Uncomplicated diabetes	$19,908.	($11,305.4 ; $28,510.6)	<0.01
Complicated diabetes	$4,282.8	(-$23,950.8 ; $32,516.3)	0.77
Renal failure	$7,397.5	(-$18,060.5 ; $32,855.5)	0.57
Coagulopathy	$90,835.4	($79,513.3 ; $102,157.5)	<0.01
Alcohol abuse	-$271.7	(-$10,883.9 ; $10,340.5)	0.96
Drug abuse	$21,112.7	($10,227.8 ; $31,997.7)	<0.01

Abbreviations: MD = mean difference, CI = confidence interval, CHF = congestive heart failure.

Table S5. Summary of Patient Inclusion and Exclusion Stratified by Year.

YEAR	TOTAL	INCLUSION	EXCLUSION	SAH	AMI	STEMI	NSTEMI
2002	36,518,331	8,165	111	8,054	277	114	162
2003	37,074,605	10,908	295	10,614	399	148	256
2004	37,496,978	11,078	323	10,755	389	150	238
2005	37,843,039	9,870	269	9,601	317	119	198
2006	38,076,556	12,356	474	11,882	424	149	275
2007	38,155,908	9,762	271	9,491	379	134	249
2008	38,210,889	11,283	455	10,828	470	130	344
2009	37,734,584	10,722	387	10,335	435	119	321
2010	37,352,013	13,494	624	12,869	415	117	304
2011	36,962,415	11,366	492	10,873	328	68	260
2012	36,484,846	11,765	470	11,295	375	55	320
2013	35,597,792	12,025	635	11,390	330	50	280
2014	35,358,818	12,280	535	11,745	455	115	340

Table S6. Summary of Patient Characteristics Across SAH and Excluded Strata.

	SAH	Excluded	
			p
	N (%)	N (%)	
Number of patients	139,732 (96.3)	5,343 (3.7)	
Demographics and CV Risk Factors			
Age, mean ± SD	54.6 ± 0.2	39.2 (22.9)	<0.001
Female	95,732 (68.5)	2,736 (51.2)	<0.001
CHF	8,666 (6.2)	150 (2.8)	<0.001
Arrhythmia	21,564 (15.4)	801 (15)	0.333
Valvular disease	3,823 (2.7)	118 (2.2)	0.218
Pulmonary circulation disorders	3,047 (2.2)	112 (2.1)	0.713
Uncomplicated hypertension	76,152 (54.5)	1,966 (36.8)	<0.001
Complicated hypertension	3,524 (2.5)	123 (2.3)	0.37
Chronic pulmonary disease	18,680 (13.4)	550 (10.3)	0.008
Uncomplicated diabetes	12,660 (9.1)	379 (7.1)	0.02
Complicated diabetes	1,118 (0.8)	16 (0.3)	0.018
Renal failure	3,128 (2.2)	118 (2.2)	0.375
Coagulopathy	6,783 (4.9)	310 (5.8)	0.242
Alcohol abuse	8,213 (5.9)	262 (4.9)	0.143
Drug abuse	7,672 (5.5)	208 (3.9)	0.013
SAH Characteristics			
Poor grade SAH	54,128 (38.7)	2,084 (39)	0.815
Clip	68,561 (49.1)	1,250 (23.4)	<0.001
Coil	72,678 (52)	4,114 (77)	<0.001
Hospital location/teaching status			<0.001
Rural	1,523 (1.1)	32 (0.6)	
Urban non-teaching	17,143 (12.3)	476 (8.9)	
Urban teaching	121,066 (86.6)	4,835 (90.5)	
Primary payer			<0.001
Private insurance	63,549 (45.5)	2,677 (50.1)	
Medicare/Medicaid	54,898 (39.3)	2,025 (37.9)	
Self-pay	14,167 (10.1)	363 (6.8)	
Other	7,118 (5.1)	278 (5.2)	
AMI Characteristics			<0.001
STEMI	1,548 (1.1)	16 (0.3)	
NSTEMI	3,549 (2.5)	59 (1.1)	
*Outcomes**			
Poor functional status at discharge	77,718 (55.6)	2,565 (48.0)	<0.001
Inpatient mortality	18,151 (13)	476 (8.9)	<0.001
Length of stay, mean ± SD	18.6 ± 0.1	18.5 ± 18.1	0.741
Total charges, mean ± SD	$263,983.3 ± $17,347.7	$295,310.5 ± $281,328.9	0.004

Table S7. Univariate Regressions for Outcomes of Interest.

	Effect estimate	95% CI	p
		AMI	
SOM	4	(3.8 – 4.4)	<0.001
DIED	2.6	(2.5 – 2.8)	<0.001
LOS	4.5	(3.6 – 5.4)	<0.001
TOTCHG	$100,122.80	($86,156.7 - $114,088.9)	<0.001
		STEMI	
SOM	5.6	(4.8 – 6.5)	<0.001
DIED	3.5	(3.1 – 3.9)	<0.001
LOS	4.6	(2.9 – 6.3)	<0.001
TOTCHG	$96,574.10	($71,163.5 - $121,984.8)	<0.001
		NSTEMI	
SOM	3.6	(3.3 – 3.9)	<0.001
DIED	2.2	(2 – 2.4)	<0.001
LOS	4.3	(3.2 – 5.4)	<0.001
TOTCHG	$100,409.00	($83,886.1 – $116,932)	<0.001

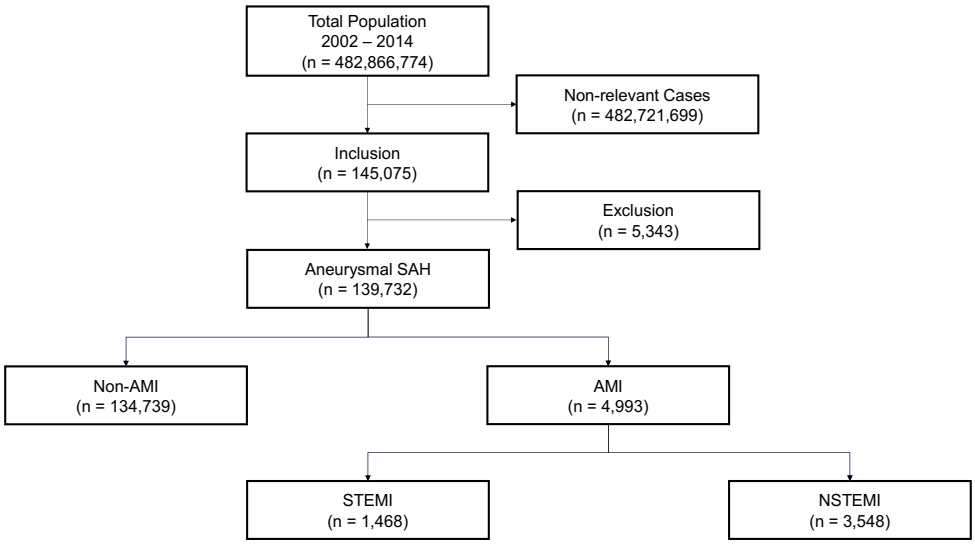


Figure S1. CONSORT Flow-Chart of Patient Selection.

SUMMARY OF CONCLUSIONS

PROJECT 1

Hyperglycemia occurs in two-thirds of all IS patients and is associated with higher volumes of tissue necrosis and worsen functional outcomes. We performed a meta-analysis of RCTs of patients with acute ischemic stroke and showed that, compared with standard glucose management strategies, insulin therapy aimed at strict glucose control is not associated with improvements in mortality, independence, or mRS scores and is associated with higher rates of symptomatic or severe hypoglycemia. Tight glycemic control was hypothesized to improve outcomes after stroke by promoting a slightly anticoagulatory profile. Based on our findings, however, it appears that factors leading to hyperglycemia (e.g. diabetes mellitus), and not hyperglycemia itself, may be the cause of worsen outcomes observed in patients with hyperglycemia. Most studies included in our study had an unblinded outcome assessment, which may limit the conclusions we made on outcomes that are highly dependent on the observer's interpretation. The length of follow-up was short for half of the included studies, limiting the number of studies in which we analyzed outcomes at ≥90 days.

PROJECT 2

Myocardial injury occurs commonly after aneurysmal subarachnoid hemorrhage (aSAH). Precise estimates of the incidence of acute myocardial infarction (AMI) after aSAH are unavailable. We performed an analysis of the National Inpatient Samples from 2002 to 2014 to estimate the incidence of AMI after aSAH. The incidence of AMI after aSAH is 3.6%, with NSTEMI as the most common type of AMI occurring after aSAH. Patients developing AMI after aSAH were older, more commonly female, had a distinct profile of cardiovascular risk factors, and more likely to have a poor SAH grade. Patients with AMI after aSAH had higher odds of poor functional status at discharge and in-hospital mortality, and a longer and more costly hospital stay after adjusting for baseline characteristics.

DISCUSSION AND PERSPECTIVES

PROJECT 1

Hyperglycemia is believed to worsen outcomes after IS through four mechanisms: 1) impaired recanalization, 2) decreased reperfusion, 3) increased reperfusion injury, and 4) direct tissue injury. Through interactions with scavenger receptors, hyperglycemia may worsen secondary brain injury by stimulating the IL-1-NRLP inflammasome pathway during acute brain injury. (11) Drugs targeting the IL-1-NRLP inflammasome pathway have shown promising brain-salvaging effects in pre-clinical models. (12) The effect of IL-1-NRLP inflammasome-targeting drugs, however, may be limited by low tissue penetration, particularly in patients in whom recanalization is not possible. (13) Alternative therapeutic strategies aiming at the modulation of the IL-1-NRLP inflammasome pathway are therefore of interest and will be a focus of my future research.

PROJECT 2

Transient left ventricular dysfunction occurs in one of every three aSAH cases and is associated with poor outcome.(14,15) Most cases of transient left ventricular dysfunction are caused by non-ischemic myocardial injury. (16) Although our results demonstrated that only a small fraction of patients with aSAH have an ischemic myocardial injury (3.6%), due to overlap in clinical findings distinguishing ischemic from non-ischemic causes of transient left ventricular dysfunction is challenging. Therefore, up to 10% of patients with transient left ventricular dysfunction after aSAH may have ischemic heart disease, making adequate diagnostic tools necessary. (17) Percutaneous coronary angiography is commonly used to rule out ischemic heart disease but is relatively contraindicated in the setting of aSAH.(18) Cardiac CT angiography may be preferable in this setting provided its use in aSAH is evaluated, which is a goal of my future research.

BIBLIOGRAPHY

1. Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, et al. An updated definition of stroke for the 21st century: A statement for healthcare professionals from the American heart association/American stroke association. Stroke. 2013;44(7):2064–89.

2. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, et al. Heart Disease and Stroke Statistics-2020 Update: A Report From the American Heart Association. Vol. 141, Circulation. 2020. 139–596 p.

3. Campbell BCV, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med. 2015;372(11):1009–18.

4. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med. 2015 Mar;372(11):1019–30.

5. Hébert M, Lesept F, Vivien D, Macrez R. The story of an exceptional serine protease, tissue-type plasminogen activator (tPA). Rev Neurol (Paris). 2016;172(3):186–97.

6. Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. N Engl J Med. 2018;378(1):11–21.

7. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, 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. Vol. 49, Stroke. 2018. 46–110 p.

8. Saber H, Navi BB, Grotta JC, Kamel H, Bambhroliya A, Vahidy FS, et al. Real-world treatment trends in endovascular stroke therapy. Stroke. 2019;50(3):683–9.

9. Lovelock CE, Rinkel GJE, Rothwell PM. Time trends in outcome of subarachnoid hemorrhage: Population-based study and systematic review. Neurology. 2010;74(19):1494–501.

10. Al-Khindi T, MacDonald RL, Schweizer TA. Cognitive and functional outcome after aneurysmal subarachnoid hemorrhage. Stroke. 2010;41(8).

11. Cerecedo-López CD, Kim-Lee JH, Hernandez D, Acosta SA, Borlongan CV. Insulin-associated neuroinflammatory pathways as therapeutic targets for traumatic brain injury. Med Hypotheses. 2014;82(2).

12. Liberale L, Diaz-Cañestro C, Bonetti NR, Paneni F, Akhmedov A, Beer JH, et al. Post-ischaemic administration of the murine Canakinumab-surrogate antibody improves outcome in experimental stroke. Eur Heart J. 2018;39(38):3511–7.

13. Fox E, Jayaprakash N, Pham TH, Rowley A, McCully CL, Pucino F, et al. The serum and cerebrospinal fluid pharmacokinetics of anakinra after intravenous administration to non-human primates. J Neuroimmunol. 2010;223(1–2):138–40.

14. Ivo van der Bilt, Djo Hasan, Renee van den Brink, Rob Groen, et al. Cardiac dysfunction after aneurysmal subarachnoid hemorrhage. Neurology. 2014;82:1–8.

15. Banki N, Kopelnik A, Tung P, Lawton MT, Gress D, Drew B, et al. Prospective analysis of prevalence, distribution, and rate of recovery of left ventricular systolic dysfunction in patients with subarachnoid hemorrhage. J Neurosurg. 2006;105(1):15–20.

16. Bybee KA, Prasad A. Stress-related cardiomyopathy syndromes. Circulation. 2008;118(4):397–409.

17. DeFilippis AP, Chapman AR, Mills NL, De Lemos JA, Arbab-Zadeh A, Newby LK, et al. Assessment and treatment of patients with type 2 myocardial infarction and acute nonischemic myocardial injury. Circulation. 2019;140(20):1661–78.

18. Ghadri JR, Wittstein IS, Prasad A, Sharkey S, Dote K, Akashi YJ, et al. International Expert Consensus Document on Takotsubo Syndrome (Part II): Diagnostic Workup, Outcome, and Management. Eur Heart J. 2018;39(22):2047–62.