

Supplementary references

1. Offner H, Subramanian S, Parker SM, Afentoulis ME, Vandenberg AA, Hurn PD. Experimental stroke induces massive, rapid activation of the peripheral immune system. *J Cereb Blood Flow Metab* 2006;26:654–665.
2. Offner H, Subramanian S, Parker SM, Wang C, Afentoulis ME, Lewis A, et al. Splenic atrophy in experimental stroke is accompanied by increased regulatory T cells and circulating macrophages. *J Immunol* 2006;176:6523–6531.
3. Gu L, Xiong X, Zhang H, Xu B, Steinberg GK, Zhao H. Distinctive effects of T cell subsets in neuronal injury induced by cocultured splenocytes in vitro and by in vivo stroke in mice. *Stroke* 2012;43:1941–1946.
4. Gu L, Xiong X, Wei D, Gao X, Krams S, Zhao H. T cells contribute to stroke-induced lymphopenia in rats. *PLoS One* 2013;8:e59602.
5. Braun JS, Prass K, Dirnagl U, Meisel A, Meisel C. Protection from brain damage and bacterial infection in murine stroke by the novel caspase-inhibitor Q-VD-OPH. *Exp Neurol* 2007;206:183–191.
6. Wong CH, Jenne CN, Lee WY, Léger C, Kubes P. Functional innervation of hepatic iNKT cells is immunosuppressive following stroke. *Science* 2011;334:101–105.
7. Kim ID, Lee H, Kim SW, Lee HK, Choi J, Han PL, et al. Alarmin HMGB1 induces systemic and brain inflammatory exacerbation in post-stroke infection rat model. *Cell Death Dis* 2018;9:426.
8. Walker PA, Shah SK, Jimenez F, Gerber MH, Xue H, Cutrone R, et al. Intravenous multipotent adult progenitor cell therapy for traumatic brain injury: preserving the blood brain barrier via an interaction with splenocytes. *Exp Neurol* 2010;225:341–352.
9. Ajmo CT Jr, Vernon DO, Collier L, Hall AA, Garbuzova-Davis S, Willing A, et al. The spleen contributes to stroke-induced neurodegeneration. *J Neurosci Res* 2008;86:2227–2234.
10. Dotson AL, Wang J, Saugstad J, Murphy SJ, Offner H. Splenectomy reduces infarct volume and neuroinflammation in male but not female mice in experimental stroke. *J Neuroimmunol* 2015;278:289–298.
11. Kim E, Yang J, Beltran CD, Cho S. Role of spleen-derived monocytes/macrophages in acute ischemic brain injury. *J Cereb Blood Flow Metab* 2014;34:1411–1419.
12. Zierath D, Shen A, Stults A, Olmstead T, Becker KJ. Splenectomy does not improve long-term outcome after stroke. *Stroke* 2017;48:497–500.
13. Belinga VF, Wu GJ, Yan FL, Limbenga EA. Splenectomy following MCAO inhibits the TLR4–NF- κ B signaling pathway and protects the brain from neurodegeneration in rats. *J Neuroimmunol* 2016;293:105–113.
14. Kharrazian D. Traumatic brain injury and the effect on the brain–gut axis. *Altern Ther Health Med* 2015;21 Suppl 3:28–32.
15. Kigerl KA, Mostacada K, Popovich PG. Gut microbiota are disease-modifying factors after traumatic spinal cord injury. *Neurotherapeutics* 2018;15:60–67.
16. Singh V, Roth S, Llovera G, Sadler R, Garzetti D, Stecher B, et al. Microbiota dysbiosis controls the neuroinflammatory response after stroke. *J Neurosci* 2016;36:7428–7440.
17. Stanley D, Moore RJ, Wong CHY. An insight into intestinal mucosal microbiota disruption after stroke. *Sci Rep* 2018;8:568.
18. Winek K, Engel O, Koduah P, Heimesaat MM, Fischer A, Bereswill S, et al. Depletion of cultivatable gut microbiota by broad-spectrum antibiotic pretreatment worsens outcome after murine stroke. *Stroke* 2016;47:1354–1363.
19. Tascilar N, Irkorucu O, Tascilar O, Comert F, Eroglu O, Bahadir B, et al. Bacterial translocation in experimental stroke: what happens to the gut barrier? *Bratisl Lek Listy* 2010;111:194–199.
20. Benakis C, Brea D, Caballero S, Faraco G, Moore J, Murphy M, et al. Commensal microbiota affects ischemic stroke outcome by regulating intestinal $\gamma\delta$ T cells. *Nat Med* 2016;22:516–523.
21. Crapser J, Ritzel R, Verma R, Venna VR, Liu F, Chauhan A, et al. Ischemic stroke induces gut permeability and enhances bacterial translocation leading to sepsis in aged mice. *Aging (Albany NY)* 2016;8:1049–1063.
22. Oyama N, Winek K, Bäcker-Koduah P, Zhang T, Dames C, Werich M, et al. Exploratory investigation of intestinal function and bacterial translocation after focal cerebral ischemia in the mouse. *Front Neurol* 2018;9:937.
23. Chamorro Á, Meisel A, Planas AM, Urra X, van de Beek D, Veltkamp R. The immunology of acute stroke. *Nat Rev Neurol* 2012;8:401–410.
24. Liu Q, Jin WN, Liu Y, Shi K, Sun H, Zhang F, et al. Brain ischemia suppresses immunity in the periphery and brain via different neurogenic innervations. *Immunity* 2017;46:474–487.
25. Johnston KC, Li JY, Lyden PD, Hanson SK, Feasby TE, Adams RJ, et al. Medical and neurological complications of ischemic stroke: experience from the RANTTAS trial. RANTTAS Investigators. *Stroke* 1998;29:447–453.
26. Chiu NL, Kaiser B, Nguyen YV, Welbourne S, Lall C, Cramer SC. The volume of the spleen and its correlates after acute

- stroke. *J Stroke Cerebrovasc Dis* 2016;25:2958–2961.
27. Vogelgesang A, Grunwald U, Langner S, Jack R, Bröker BM, Kessler C, et al. Analysis of lymphocyte subsets in patients with stroke and their influence on infection after stroke. *Stroke* 2008;39:237–241.
 28. Mocco J, Wilson DA, Komotar RJ, Sughrue ME, Coates K, Sacco RL, et al. Alterations in plasma complement levels following human ischemic stroke. *Neurosurgery* 2006;59:1–6.
 29. Planas AM, Gómez-Choco M, Urrea X, Gorina R, Caballero M, Chamorro Á. Brain-derived antigens in lymphoid tissue of patients with acute stroke. *J Immunol* 2012;188:2156–2163.
 30. Yang QW, Lu FL, Zhou Y, Wang L, Zhong Q, Lin S, et al. HMBG1 mediates ischemia-reperfusion injury by TRIF-adaptor independent toll-like receptor 4 signaling. *J Cereb Blood Flow Metab* 2011;31:593–605.
 31. Liesz A, Dalpke A, Mracsko E, Antoine DJ, Roth S, Zhou W, et al. DAMP signaling is a key pathway inducing immune modulation after brain injury. *J Neurosci* 2015;35:583–598.
 32. Harms H, Prass K, Meisel C, Klehmet J, Rogge W, Drenckhahn C, et al. Preventive antibacterial therapy in acute ischemic stroke: a randomized controlled trial. *PLoS One* 2008;3:e2158.
 33. Hug A, Dalpke A, Wiczorek N, Giese T, Lorenz A, Auffarth G, et al. Infarct volume is a major determiner of post-stroke immune cell function and susceptibility to infection. *Stroke* 2009;40:3226–3232.
 34. Hernández-Jiménez E, Gutierrez-Fernández M, Cubillos-Zapata C, Otero-Ortega L, Rodríguez-Frutos B, Toledano V, et al. Circulating monocytes exhibit an endotoxin tolerance status after acute ischemic stroke: mitochondrial DNA as a putative explanation for poststroke infections. *J Immunol* 2017;198:2038–2046.
 35. Hoffmann S, Harms H, Ulm L, Nabavi DG, Mackert BM, Schmehl I, et al. Stroke-induced immunodepression and dysphagia independently predict stroke-associated pneumonia: the PREDICT study. *J Cereb Blood Flow Metab* 2017;37:3671–3682.
 36. van de Beek D, Wijdsicks EF, Vermeij FH, de Haan RJ, Prins JM, Spanjaard L, et al. Preventive antibiotics for infections in acute stroke: a systematic review and meta-analysis. *Arch Neurol* 2009;66:1076–1081.
 37. Badve MS, Zhou Z, Anderson CS, Hackett ML. Effectiveness and safety of antibiotics for preventing pneumonia and improving outcome after acute stroke: systematic review and meta-analysis. *J Stroke Cerebrovasc Dis* 2018;27:3137–3147.
 38. Yin J, Liao SX, He Y, Wang S, Xia GH, Liu FT, et al. Dysbiosis of gut microbiota with reduced trimethylamine-n-oxide level in patients with large-artery atherosclerotic stroke or transient ischemic attack. *J Am Heart Assoc* 2015;4:e002699.
 39. Stanley D, Mason LJ, Mackin KE, Srikhanta YN, Lyras D, Prakash MD, et al. Translocation and dissemination of commensal bacteria in post-stroke infection. *Nat Med* 2016;22:1277–1284.
 40. Yamashiro K, Tanaka R, Urabe T, Ueno Y, Yamashiro Y, Nomoto K, et al. Gut dysbiosis is associated with metabolism and systemic inflammation in patients with ischemic stroke. *PLoS One* 2017;12:e0171521.
 41. Yamashiro K, Tanaka R, Urabe T, Ueno Y, Yamashiro Y, Nomoto K, et al. Correction: gut dysbiosis is associated with metabolism and systemic inflammation in patients with ischemic stroke. *PLoS One* 2017;12:e0176062.
 42. Prass K, Meisel C, Höflich C, Braun J, Halle E, Wolf T, et al. Stroke-induced immunodeficiency promotes spontaneous bacterial infections and is mediated by sympathetic activation reversal by poststroke T helper cell type 1-like immunostimulation. *J Exp Med* 2003;198:725–736.
 43. Ajmo CT Jr, Collier LA, Leonardo CC, Hall AA, Green SM, Womble TA, et al. Blockade of adrenoceptors inhibits the splenic response to stroke. *Exp Neurol* 2009;218:47–55.
 44. Yan FL, Zhang JH. Role of the sympathetic nervous system and spleen in experimental stroke-induced immunodepression. *Med Sci Monit* 2014;20:2489–2496.
 45. Mracsko E, Liesz A, Karcher S, Zorn M, Bari F, Veltkamp R. Differential effects of sympathetic nervous system and hypothalamic-pituitary-adrenal axis on systemic immune cells after severe experimental stroke. *Brain Behav Immun* 2014;41:200–209.
 46. Ay I, Sorensen AG, Ay H. Vagus nerve stimulation reduces infarct size in rat focal cerebral ischemia: an unlikely role for cerebral blood flow. *Brain Res* 2011;1392:110–115.
 47. Han Z, Shen F, He Y, Degos V, Camus M, Maze M, et al. Activation of α -7 nicotinic acetylcholine receptor reduces ischemic stroke injury through reduction of pro-inflammatory macrophages and oxidative stress. *PLoS One* 2014;9:e105711.
 48. Engel O, Akyüz L, da Costa Goncalves AC, Winek K, Dames C, Thielke M, et al. Cholinergic pathway suppresses pulmonary innate immunity facilitating pneumonia after stroke. *Stroke* 2015;46:3232–3240.
 49. Chamorro A, Amaro S, Vargas M, Obach V, Cervera A, Gómez-Choco M, et al. Catecholamines, infection, and death in acute ischemic stroke. *J Neurol Sci* 2007;252:29–35.

50. McCulloch L, Smith CJ, McColl BW. Adrenergic-mediated loss of splenic marginal zone B cells contributes to infection susceptibility after stroke. *Nat Commun* 2017;8:15051.
51. Dzedzic T, Slowik A, Pera J, Szczudlik A. Beta-blockers reduce the risk of early death in ischemic stroke. *J Neurol Sci* 2007;252:53-56.
52. Sykora M, Siarnik P, Diedler J; VISTA Acute Collaborators. β -Blockers, pneumonia, and outcome after ischemic stroke: evidence from virtual international stroke trials archive. *Stroke* 2015;46:1269-1274.
53. De Raedt S, Haentjens P, De Smedt A, Brouns R, Uyttenboogaart M, Luijckx GJ, et al. Pre-stroke use of beta-blockers does not affect ischaemic stroke severity and outcome. *Eur J Neurol* 2012;19:234-240.
54. Maier IL, Becker JC, Leyhe JR, Schnieder M, Behme D, Psychogios MN, et al. Influence of beta-blocker therapy on the risk of infections and death in patients at high risk for stroke induced immunodepression. *PLoS One* 2018;13:e0196174.
55. Westendorp WF, Vermeij JD, Brouwer MC, Roos YB, Nederkoorn PJ, van de Beek D, et al. Pre-stroke use of beta-blockers does not lower post-stroke infection rate: an exploratory analysis of the preventive antibiotics in stroke study. *Cerebrovasc Dis* 2016;42:506-511.
56. Starr JB, Tirschwell DL, Becker KJ. Increased infections with β -blocker use in ischemic stroke, a β 2-receptor mediated process? *Neurol Sci* 2017;38:967-974.
57. Harms H, Reimnitz P, Bohner G, Werich T, Klingebiel R, Meisel C, et al. Influence of stroke localization on autonomic activation, immunodepression, and post-stroke infection. *Cerebrovasc Dis* 2011;32:552-560.
58. Haeusler KG, Schmidt WU, Föhring F, Meisel C, Helms T, Jungehulsing GJ, et al. Cellular immunodepression preceding infectious complications after acute ischemic stroke in humans. *Cerebrovasc Dis* 2008;25:50-58.
59. Barugh AJ, Gray P, Shenkin SD, MacLulich AM, Mead GE. Cortisol levels and the severity and outcomes of acute stroke: a systematic review. *J Neurol* 2014;261:533-545.
60. Prass K, Braun JS, Dirnagl U, Meisel C, Meisel A. Stroke propagates bacterial aspiration to pneumonia in a model of cerebral ischemia. *Stroke* 2006;37:2607-2612.
61. Suda S, Aoki J, Shimoyama T, Suzuki K, Sakamoto Y, Katanoto T, et al. Stroke-associated infection independently predicts 3-month poor functional outcome and mortality. *J Neurol* 2018;265:370-375.
62. Walter U, Knoblich R, Steinhagen V, Donat M, Benecke R, Kloth A. Predictors of pneumonia in acute stroke patients admitted to a neurological intensive care unit. *J Neurol* 2007;254:1323-1329.
63. Lakshminarayan K, Tsai AW, Tong X, Vazquez G, Peacock JM, George MG, et al. Utility of dysphagia screening results in predicting poststroke pneumonia. *Stroke* 2010;41:2849-2854.
64. Kalra L, Irshad S, Hodsoll J, Simpson M, Gulliford M, Smithard D, et al. Prophylactic antibiotics after acute stroke for reducing pneumonia in patients with dysphagia (STROKE-INF): a prospective, cluster-randomised, open-label, masked endpoint, controlled clinical trial. *Lancet* 2015;386:1835-1844.
65. Xi YG, Tian X, Chen WQ, Zhang S, Zhang S, Ren WD, et al. Antibiotic prophylaxis for infections in patients with acute stroke: a systematic review and meta-analysis of randomized controlled trials. *Oncotarget* 2017;8:81075-81087.
66. Kelly J, Rudd A, Lewis RR, Coshall C, Moody A, Hunt BJ. Venous thromboembolism after acute ischemic stroke: a prospective study using magnetic resonance direct thrombus imaging. *Stroke* 2004;35:2320-2325.
67. Pilato F, Calandrelli R, Profice P, Della Marca G, Broccolini A, Bello G, et al. Pulmonary embolism in a stroke patient after systemic thrombolysis: clinical decisions and literature review. *J Stroke Cerebrovasc Dis* 2013;22:e667-e670.
68. Pongmoragot J, Rabinstein AA, Nilanont Y, Swartz RH, Zhou L, Saposnik G, et al. Pulmonary embolism in ischemic stroke: clinical presentation, risk factors, and outcome. *J Am Heart Assoc* 2013;2:e000372.
69. Bembenek JP, Karlinski M, Kobayashi A, Czlonkowska A. Deep venous thrombosis in acute stroke patients. *Clin Appl Thromb Hemost* 2012;18:258-264.
70. Douds GL, Hellkamp AS, Olson DM, Fonarow GC, Smith EE, Schwamm LH, et al. Venous thromboembolism in the Get With The Guidelines-Stroke acute ischemic stroke population: incidence and patterns of prophylaxis. *J Stroke Cerebrovasc Dis* 2014;23:123-129.
71. Rinde LB, Småbrekke B, Mathiesen EB, Løchen ML, Njølstad I, Hald EM, et al. Ischemic stroke and risk of venous thromboembolism in the general population: the Tromsø study. *J Am Heart Assoc* 2016;5:e004311.
72. Sandercock PA, Counsell C, Kane EJ. Anticoagulants for acute ischaemic stroke. *Cochrane Database Syst Rev* 2015;2015:CD000024.
73. CLOTS (Clots in Legs Or sTockings after Stroke) Trials Collaboration, Dennis M, Sandercock P, Reid J, Graham C, Forbes J, et al. Effectiveness of intermittent pneumatic compression in reduction of risk of deep vein thrombosis in patients who have had a stroke (CLOTS 3): a multicentre randomised controlled trial. *Lancet* 2013;382:516-

- 524.
74. Dennis M, Sandercock P, Graham C, Forbes J; CLOTS (Clots in Legs Or sTockings after Stroke) Trials Collaboration, Smith J. The Clots in Legs Or sTockings after Stroke (CLOTS) 3 trial: a randomised controlled trial to determine whether or not intermittent pneumatic compression reduces the risk of post-stroke deep vein thrombosis and to estimate its cost-effectiveness. *Health Technol Assess* 2015;19:1-90.
 75. Morelli VM, Sejrup JK, Småbrekke B, Rinde LB, Grimnes G, Isaksen T, et al. The role of stroke as a trigger for incident venous thromboembolism: results from a population-based case-crossover study. *TH Open* 2019;3:e50-e57.
 76. Ersoz M, Ulusoy H, Oktar MA, Akyuz M. Urinary tract infection and bacteriuria in stroke patients: frequencies, pathogen microorganisms, and risk factors. *Am J Phys Med Rehabil* 2007;86:734-741.
 77. Indredavik B, Rohweder G, Naalsund E, Lydersen S. Medical complications in a comprehensive stroke unit and an early supported discharge service. *Stroke* 2008;39:414-420.
 78. Stott DJ, Falconer A, Miller H, Tilston JC, Langhorne P. Urinary tract infection after stroke. *QJM* 2009;102:243-249.
 79. Ifejika-Jones NL, Peng H, Noser EA, Francisco GE, Grotta JC. Hospital-acquired symptomatic urinary tract infection in patients admitted to an academic stroke center affects discharge disposition. *PM R* 2013;5:9-15.
 80. Huang WC, Wann SR, Lin SL, Kunin CM, Kung MH, Lin CH, et al. Catheter-associated urinary tract infections in intensive care units can be reduced by prompting physicians to remove unnecessary catheters. *Infect Control Hosp Epidemiol* 2004;25:974-978.
 81. Topal J, Conklin S, Camp K, Morris V, Balcezak T, Herbert P. Prevention of nosocomial catheter-associated urinary tract infections through computerized feedback to physicians and a nurse-directed protocol. *Am J Med Qual* 2005;20:121-126.
 82. Titsworth WL, Hester J, Correia T, Reed R, Williams M, Guin P, et al. Reduction of catheter-associated urinary tract infections among patients in a neurological intensive care unit: a single institution's success. *J Neurosurg* 2012;116:911-920.
 83. Chen SC, Chen PY, Chen GC, Chuang SY, Tzeng IS, Lin SK. Portable bladder ultrasound reduces incidence of urinary tract infection and shortens hospital length of stay in patients with acute ischemic stroke. *J Cardiovasc Nurs* 2018;33:551-558.
 84. Muramatsu K, Fujino Y, Kubo T, Otani M, Fushimi K, Matsuda S. Efficacy of antimicrobial catheters for prevention of catheter-associated urinary tract infection in acute cerebral infarction. *J Epidemiol* 2018;28:54-58.
 85. Hachinski VC, Oppenheimer SM, Wilson JX, Guiraudon C, Cechetto DF. Asymmetry of sympathetic consequences of experimental stroke. *Arch Neurol* 1992;49:697-702.
 86. Dziedzic T, Slowik A, Szczudlik A. Urine albumin excretion in acute ischaemic stroke is related to serum interleukin-6. *Clin Chem Lab Med* 2004;42:182-185.
 87. Thomas LH, Coupe J, Cross LD, Tan AL, Watkins CL. Interventions for treating urinary incontinence after stroke in adults. *Cochrane Database Syst Rev* 2019;2:CD004462.
 88. Pettersen R, Wyller TB. Prognostic significance of micturition disturbances after acute stroke. *J Am Geriatr Soc* 2006;54:1878-1884.
 89. Lee SJ, Lee DG. Relationship between kidney dysfunction and ischemic stroke outcomes: albuminuria, but not estimated glomerular filtration rate, is associated with the risk of further vascular events and mortality after stroke. *PLoS One* 2016;11:e0155939.
 90. Tsagalis G, Akrivos T, Alevizaki M, Manios E, Stamatellopoulos K, Laggouranis A, et al. Renal dysfunction in acute stroke: an independent predictor of long-term all combined vascular events and overall mortality. *Nephrol Dial Transplant* 2009;24:194-200.
 91. Shrestha P, Thapa S, Shrestha S, Lohani S, Bk S, MacCormac O, et al. Renal impairment in stroke patients: a comparison between the haemorrhagic and ischemic variants. Version 2. *F1000Res* 2017;6:1531.
 92. Khatri M, Himmelfarb J, Adams D, Becker K, Longstreth WT, Tirschwell DL. Acute kidney injury is associated with increased hospital mortality after stroke. *J Stroke Cerebrovasc Dis* 2014;23:25-30.
 93. Nadkarni GN, Patel AA, Konstantinidis I, Mahajan A, Agarwal SK, Kamat S, et al. Dialysis requiring acute kidney injury in acute cerebrovascular accident hospitalizations. *Stroke* 2015;46:3226-3231.
 94. Zorrilla-Vaca A, Ziai W, Connolly ES Jr, Geocadin R, Thompson R, Rivera-Lara L. Acute kidney injury following acute ischemic stroke and intracerebral hemorrhage: a meta-analysis of prevalence rate and mortality risk. *Cerebrovasc Dis* 2018;45:1-9.
 95. Arnold J, Ng KP, Sims D, Gill P, Cockwell P, Ferro C. Incidence and impact on outcomes of acute kidney injury after a stroke: a systematic review and meta-analysis. *BMC Nephrol* 2018;19:283.
 96. Wu CL, Tsai CC, Kor CT, Tarng DC, Lian leB, Yang TH, et al. Stroke and risks of development and progression of kidney

- diseases and end-stage renal disease: a nationwide population-based cohort study. *PLoS One* 2016;11:e0158533.
97. Jia S, Xia Q, Zhang B, Wang L. Involvement of the paraventricular nucleus in the occurrence of arrhythmias in middle cerebral artery occlusion rats. *J Stroke Cerebrovasc Dis* 2015;24:844-851.
 98. Bieber M, Werner RA, Tanai E, Hofmann U, Higuchi T, Schuh K, et al. Stroke-induced chronic systolic dysfunction driven by sympathetic overactivity. *Ann Neurol* 2017;82:729-743.
 99. Daniele O, Caravaglios G, Fierro B, Natalè E. Stroke and cardiac arrhythmias. *J Stroke Cerebrovasc Dis* 2002;11:28-33.
 100. Di Pasquale G, Pinelli G, Grazi P, Andreoli A, Corbelli C, Manini GL, et al. Incidence of silent myocardial ischaemia in patients with cerebral ischaemia. *Eur Heart J* 1988;9 Suppl N:104-107.
 101. Adams RJ, Chimowitz MI, Alpert JS, Awad IA, Cerqueria MD, Fayad P, et al. Coronary risk evaluation in patients with transient ischemic attack and ischemic stroke: a scientific statement for healthcare professionals from the Stroke Council and the Council on Clinical Cardiology of the American Heart Association/American Stroke Association. *Stroke* 2003;34:2310-2322.
 102. Ay H, Koroshetz WJ, Benner T, Vangel MG, Melinsky C, Arsava EM, et al. Neuroanatomic correlates of stroke-related myocardial injury. *Neurology* 2006;66:1325-1329.
 103. Touzé E, Varenne O, Chatellier G, Peyrard S, Rothwell PM, Mas JL. Risk of myocardial infarction and vascular death after transient ischemic attack and ischemic stroke: a systematic review and meta-analysis. *Stroke* 2005;36:2748-2755.
 104. Joundi RA, Rabinstein AA, Nikneshan D, Tu JV, Fang J, Holloway R, et al. Cardiac arrest in acute ischemic stroke: incidence, predisposing factors, and clinical outcomes. *J Stroke Cerebrovasc Dis* 2016;25:1644-1652.
 105. Prosser J, MacGregor L, Lees KR, Diener HC, Hacke W, Davis S, et al. Predictors of early cardiac morbidity and mortality after ischemic stroke. *Stroke* 2007;38:2295-2302.
 106. Yoshimura S, Toyoda K, Ohara T, Nagasawa H, Ohtani N, Kuwashiro T, et al. Takotsubo cardiomyopathy in acute ischemic stroke. *Ann Neurol* 2008;64:547-554.
 107. Jung JM, Kim JG, Kim JB, Cho KH, Yu S, Oh K, et al. Takotsubo-like myocardial dysfunction in ischemic stroke: a hospital-based registry and systematic literature review. *Stroke* 2016;47:2729-2736.
 108. Million H, Faouzi M, Cordier M, D'Ambrogio-Remillard S, Eskandari A, Michel P. Characteristics and early and long-term outcome in patients with acute ischemic stroke and low ejection fraction. *Int J Cardiol* 2013;168:1082-1087.
 109. Colivicchi F, Bassi A, Santini M, Caltagirone C. Cardiac autonomic derangement and arrhythmias in right-sided stroke with insular involvement. *Stroke* 2004;35:2094-2098.
 110. Laowattana S, Zeger SL, Lima JA, Goodman SN, Wittstein IS, Oppenheimer SM. Left insular stroke is associated with adverse cardiac outcome. *Neurology* 2006;66:477-483.
 111. Korpelainen JT, Huikuri HV, Sotaniemi KA, Myllylä VV. Abnormal heart rate variability reflecting autonomic dysfunction in brainstem infarction. *Acta Neurol Scand* 1996;94:337-342.
 112. Francica JV, Bigongiari A, Mochizuki L, Scapini KB, Moraes OA, Mostarda C, et al. Cardiac autonomic dysfunction in chronic stroke women is attenuated after submaximal exercise test, as evaluated by linear and nonlinear analysis. *BMC Cardiovasc Disord* 2015;15:105.
 113. Tahsili-Fahadan P, Geocadin RG. Heart-brain axis: effects of neurologic injury on cardiovascular function. *Circ Res* 2017;120:559-572.
 114. Xu X, Zhu Y, Chuai J. Changes in serum ghrelin and small intestinal motility in rats with ischemic stroke. *Anat Rec (Hoboken)* 2012;295:307-312.
 115. Feng W, Vasquez G, Suri MF, Lakshminarayan K, Qureshi AI. Repeated-measures analysis of the National Institute of Neurological Disorders and Stroke rt-PA stroke trial. *J Stroke Cerebrovasc Dis* 2011;20:241-246.
 116. Hsu HL, Lin YH, Huang YC, Weng HH, Lee M, Huang WY, et al. Gastrointestinal hemorrhage after acute ischemic stroke and its risk factors in Asians. *Eur Neurol* 2009;62:212-218.
 117. Chen CM, Hsu HC, Chuang YW, Chang CH, Lin CH, Hong CZ. Study on factors affecting the occurrence of upper gastrointestinal bleeding in elderly acute stroke patients undergoing rehabilitation. *J Nutr Health Aging* 2011;15:632-636.
 118. Ogata T, Kamouchi M, Matsuo R, Hata J, Kuroda J, Ago T, et al. Gastrointestinal bleeding in acute ischemic stroke: recent trends from the fukuoka stroke registry. *Cerebrovasc Dis Extra* 2014;4:156-164.
 119. Li J, Yuan M, Liu Y, Zhao Y, Wang J, Guo W. Incidence of constipation in stroke patients: a systematic review and meta-analysis. *Medicine (Baltimore)* 2017;96:e7225.
 120. Harari D, Coshall C, Rudd AG, Wolfe CD. New-onset fecal incontinence after stroke: prevalence, natural history, risk factors, and impact. *Stroke* 2003;34:144-150.
 121. Schaller BJ, Graf R, Jacobs AH. Pathophysiological changes of the gastrointestinal tract in ischemic stroke. *Am J Gastroenterol* 2006;101:1655-1665.

122. Yi JH, Chun MH, Kim BR, Han EY, Park JY. Bowel function in acute stroke patients. *Ann Rehabil Med* 2011;35:337-343.
123. Ottani A, Giuliani D, Mioni C, Galantucci M, Minutoli L, Bitto A, et al. Vagus nerve mediates the protective effects of melanocortins against cerebral and systemic damage after ischemic stroke. *J Cereb Blood Flow Metab* 2009;29:512-523.
124. Puchowicz MA, Zechel JL, Valerio J, Emancipator DS, Xu K, Pundik S, et al. Neuroprotection in diet-induced ketotic rat brain after focal ischemia. *J Cereb Blood Flow Metab* 2008;28:1907-1916.
125. Koch K, Berressem D, Konietzka J, Thinnies A, Eckert GP, Klein J. Hepatic ketogenesis induced by middle cerebral artery occlusion in mice. *J Am Heart Assoc* 2017;6:e005556.
126. Wang YY, Lin SY, Chuang YH, Sheu WH, Tung KC, Chen CJ. Activation of hepatic inflammatory pathways by catecholamines is associated with hepatic insulin resistance in male ischemic stroke rats. *Endocrinology* 2014;155:1235-1246.
127. Pineda S, Bang OY, Saver JL, Starkman S, Yun SW, Liebeskind DS, et al. Association of serum bilirubin with ischemic stroke outcomes. *J Stroke Cerebrovasc Dis* 2008;17:147-152.
128. Luo Y, Li J, Zhang J, Xu Y. Elevated bilirubin after acute ischemic stroke linked to the stroke severity. *Int J Dev Neurosci* 2013;31:634-638.
129. Muscari A, Collini A, Fabbri E, Giovagnoli M, Napoli C, Rossi V, et al. Changes of liver enzymes and bilirubin during ischemic stroke: mechanisms and possible significance. *BMC Neurol* 2014;14:122.
130. Zhu CZ, Auer RN. Optimal blood glucose levels while using insulin to minimize the size of infarction in focal cerebral ischemia. *J Neurosurg* 2004;101:664-668.
131. Szczudlik A, Slowik A, Turaj W, Wyrwicz-Petkow U, Pera J, Dziedzic T, et al. Transient hyperglycemia in ischemic stroke patients. *J Neurol Sci* 2001;189:105-111.
132. Baird TA, Parsons MW, Phan T, Butcher KS, Desmond PM, Tress BM, et al. Persistent poststroke hyperglycemia is independently associated with infarct expansion and worse clinical outcome. *Stroke* 2003;34:2208-2214.
133. Vancheri F, Curcio M, Burgio A, Salvaggio S, Gruttadauria G, Lunetta MC, et al. Impaired glucose metabolism in patients with acute stroke and no previous diagnosis of diabetes mellitus. *QJM* 2005;98:871-878.
134. Ntaios G, Egli M, Faouzi M, Michel P. J-shaped association between serum glucose and functional outcome in acute ischemic stroke. *Stroke* 2010;41:2366-2370.
135. Gray CS, Hildreth AJ, Alberti GK, O'Connell JE; GIST Collaboration. Poststroke hyperglycemia: natural history and immediate management. *Stroke* 2004;35:122-126.
136. Bruno A, Kent TA, Coull BM, Shankar RR, Saha C, Becker KJ, et al. Treatment of hyperglycemia in ischemic stroke (THIS): a randomized pilot trial. *Stroke* 2008;39:384-389.
137. Bruno A, Durkalski VL, Hall CE, Juneja R, Barsan WG, Janis S, 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;9:246-251.
138. Johnston KC, Bruno A, Pauls Q, Hall CE, Barrett KM, Barsan W, et al. Intensive vs standard treatment of hyperglycemia and functional outcome in patients with acute ischemic stroke: the SHINE randomized clinical trial. *JAMA* 2019;322:326-335.
139. Sadana P, Coughlin L, Burke J, Woods R, Mdzinarishvili A. Anti-edema action of thyroid hormone in MCAO model of ischemic brain stroke: possible association with AQP4 modulation. *J Neurol Sci* 2015;354:37-45.
140. Zhang Y, Meyer MA. Clinical analysis on alteration of thyroid hormones in the serum of patients with acute ischemic stroke. *Stroke Res Treat* 2010;2010:290678.
141. Cho HJ, Kim SS, Sung SM, Jung DS. Impact of thyroid autoantibodies on functional outcome in patients with acute ischemic stroke. *J Stroke Cerebrovasc Dis* 2014;23:1915-1920.
142. Meng H, Liu T, Borjigin J, Wang MM. Ischemic stroke destabilizes circadian rhythms. *J Circadian Rhythms* 2008;6:9.
143. Bhattacharya P, Pandey AK, Paul S, Patnaik R. Melatonin renders neuroprotection by protein kinase C mediated aquaporin-4 inhibition in animal model of focal cerebral ischemia. *Life Sci* 2014;100:97-109.
144. Kilic E, Kilic U, Yulug B, Hermann DM, Reiter RJ. Melatonin reduces disseminate neuronal death after mild focal ischemia in mice via inhibition of caspase-3 and is suitable as an add-on treatment to tissue-plasminogen activator. *J Pineal Res* 2004;36:171-176.
145. Kilic U, Kilic E, Reiter RJ, Bassetti CL, Hermann DM. Signal transduction pathways involved in melatonin-induced neuroprotection after focal cerebral ischemia in mice. *J Pineal Res* 2005;38:67-71.
146. Manev H, Uz T, Kharlamov A, Joo JY. Increased brain damage after stroke or excitotoxic seizures in melatonin-deficient rats. *FASEB J* 1996;10:1546-1551.
147. Ritzenthaler T, Nighoghossian N, Berthiller J, Schott AM, Cho TH, Derex L, et al. Nocturnal urine melatonin and 6-sulphatoxymelatonin excretion at the acute stage of ischaemic stroke. *J Pineal Res* 2009;46:349-352.

148. Vinogradov OI, Ivanova DS, Davidov NP, Kuznetsov AN. Melatonin in the correction of sleep in post-stroke patients. *Zh Nevrol Psikhiatr Im S S Korsakova* 2015;115:86-89.
149. Borschmann KN, Rewell SS, Iuliano S, Ghasem-Zadeh A, Davey RA, Ho H, et al. Reduced bone formation markers, and altered trabecular and cortical bone mineral densities of non-paretic femurs observed in rats with ischemic stroke: a randomized controlled pilot study. *PLoS One* 2017;12:e0172889.
150. Vignaux G, Ndong JD, Perrien DS, Elefteriou F. Inner ear vestibular signals regulate bone remodeling via the sympathetic nervous system. *J Bone Miner Res* 2015;30:1103-1111.
151. Kanis J, Oden A, Johnell O. Acute and long-term increase in fracture risk after hospitalization for stroke. *Stroke* 2001;32:702-706.
152. Pang MY, Eng JJ. Muscle strength is a determinant of bone mineral content in the hemiparetic upper extremity: implications for stroke rehabilitation. *Bone* 2005;37:103-111.
153. Pang MY, Ashe MC, Eng JJ. Muscle weakness, spasticity and disuse contribute to demineralization and geometric changes in the radius following chronic stroke. *Osteoporos Int* 2007;18:1243-1252.
154. Kapral MK, Fang J, Alibhai SM, Cram P, Cheung AM, Casaubon LK, et al. Risk of fractures after stroke: results from the Ontario Stroke Registry. *Neurology* 2017;88:57-64.
155. Borschmann K, Iuliano S, Ghasem-Zadeh A, Churilov L, Pang MYC, Bernhardt J. Upright activity and higher motor function may preserve bone mineral density within 6 months of stroke: a longitudinal study. *Arch Osteoporos* 2018;13:5.
156. Desgeorges MM, Devillard X, Toutain J, Divoux D, Castells J, Bernaudin M, et al. Molecular mechanisms of skeletal muscle atrophy in a mouse model of cerebral ischemia. *Stroke* 2015;46:1673-1680.
157. Springer J, Schust S, Peske K, Tschirner A, Rex A, Engel O, et al. Catabolic signaling and muscle wasting after acute ischemic stroke in mice: indication for a stroke-specific sarcopenia. *Stroke* 2014;45:3675-3683.
158. Sen CK, Khanna S, Harris H, Stewart R, Balch M, Heigel M, et al. Robot-assisted mechanical therapy attenuates stroke-induced limb skeletal muscle injury. *FASEB J* 2017;31:927-936.
159. Desgeorges MM, Devillard X, Toutain J, Castells J, Divoux D, Arnould DF, et al. Pharmacological inhibition of myostatin improves skeletal muscle mass and function in a mouse model of stroke. *Sci Rep* 2017;7:14000.
160. Jørgensen L, Jacobsen BK. Changes in muscle mass, fat mass, and bone mineral content in the legs after stroke: a 1 year prospective study. *Bone* 2001;28:655-659.
161. Benecke R, Berthold A, Conrad B. Denervation activity in the EMG of patients with upper motor neuron lesions: time course, local distribution and pathogenetic aspects. *J Neurol* 1983;230:143-151.
162. De Deyne PG, Hafer-Macko CE, Ivey FM, Ryan AS, Macko RF. Muscle molecular phenotype after stroke is associated with gait speed. *Muscle Nerve* 2004;30:209-215.
163. Ryan AS, Ivey FM, Prior S, Li G, Hafer-Macko C. Skeletal muscle hypertrophy and muscle myostatin reduction after resistive training in stroke survivors. *Stroke* 2011;42:416-420.
164. Scherbakov N, von Haehling S, Anker SD, Dirnagl U, Doehner W. Stroke induced Sarcopenia: muscle wasting and disability after stroke. *Int J Cardiol* 2013;170:89-94.
165. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, et al. Heart disease and stroke statistics: 2019 update. A report from the American Heart Association. *Circulation* 2019;139:e56-e528.
166. GBD 2016 Neurology Collaborators. Global, regional, and national burden of neurological disorders, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* 2019;18:459-480.
167. GBD 2016 Stroke Collaborators. Global, regional, and national burden of stroke, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* 2019;18:439-458.
168. 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. *Stroke* 2018;49:e46-e110.
169. Pierot L, Jayaraman MV, Szikora I, Hirsch JA, Baxter B, Miyachi S, et al. Standards of practice in acute ischemic stroke intervention: international recommendations. *J Neurointerv Surg* 2018;10:1121-1126.
170. Sacks D, Baxter B, Campbell BCV, Carpenter JS, Cognard C, Dippel D, et al. Multisociety consensus quality improvement revised consensus statement for endovascular therapy of acute ischemic stroke: from the American Association of Neurological Surgeons (AANS), American Society of Neuroradiology (ASNR), Cardiovascular and Interventional Radiology Society of Europe (CIRSE), Canadian In-

- terventional Radiology Association (CIRA), Congress of Neurological Surgeons (CNS), European Society of Minimally Invasive Neurological Therapy (ESMINT), European Society of Neuroradiology (ESNR), European Stroke Organization (ESO), Society for Cardiovascular Angiography and Interventions (SCAI), Society of Interventional Radiology (SIR), Society of NeuroInterventional Surgery (SNIS), and World Stroke Organization (WSO). *J Vasc Interv Radiol* 2018;29:441-453.
171. Johnson W, Onuma O, Owolabi M, Sachdev S. Stroke: a global response is needed. *Bull World Health Organ* 2016;94:634-634A.
172. Winstein CJ, Stein J, Arena R, Bates B, Cherney LR, Cramer SC, et al. Guidelines for adult stroke rehabilitation and recovery: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2016;47:e98-e169.
173. Platz T. Evidence-based guidelines and clinical pathways in stroke rehabilitation-an international perspective. *Front Neurol* 2019;10:200.