Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION
American Stroke Association
A Division of American Heart Association

Guidelines for the Prevention of Stroke in Patients With Stroke or Transient Ischemic Attack. A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

Karen L. Furie, Scott E. Kasner, Robert J. Adams, Gregory W. Albers, Ruth L. Bush, Susan C. Fagan, Jonathan L. Halperin, S. Claiborne Johnston, Irene Katzan, Walter N. Kernan, Pamela H. Mitchell, Bruce Ovbiagele, Yuko Y. Palesch, Ralph L. Sacco, Lee H. Schwamm, Sylvia Wassertheil-Smoller, Tanya N. Turan, Deidre Wentworth and on behalf of the American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Clinical Cardiology, and Interdisciplinary Council on Quality of Care and Outcomes Research

Stroke published online Oct 21, 2010;
DOI: 10.1161/STR.0b013e3181f7d043
Stroke is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0039-2499. Online ISSN: 1524-4628

was compared with medical treatment alone indicate trends toward better outcomes with closure.[361,362,370] Windecker et al reported a very high 3-year event rate of 33.2% in 44 medically treated patients compared with 7.3% in 59 similar patients treated with PFO closure.[370] The generally low rates of stroke in the closure series, the lack of robust outcome differences in the 3 nonrandomized comparison studies, and the overall absence of controlled comparisons of closure strategies with medical treatment alone, reinforce the need to complete randomized clinical trials comparing closure with medical therapy. A 2009 statement from the AHA/ASA/ACC strongly encourages all clinicians involved in the care of appropriate patients with cryptogenic stroke and PFO—cardiologists, neurologists, internists, radiologists, and surgeons—to consider referral for enrollment in these landmark trials to expedite their completion and help resolve the uncertainty regarding optimal care for this condition.[371]

Recommendations

1. For patients with an ischemic stroke or TIA and a PFO, antiplatelet therapy is reasonable *(Class IIa; Level of Evidence B)*.
2. There are insufficient data to establish whether anticoagulation is equivalent or superior to aspirin for secondary stroke prevention in patients with PFO *(Class IIb; Level of Evidence B)*. (New recommendation)
3. There are insufficient data to make a recommendation regarding PFO closure in patients with stroke and PFO *(Class IIb; Level of Evidence C)* (Table 10).

C. Hyperhomocysteinemia

Cohort and case-control studies have consistently demonstrated a 2-fold greater risk of stroke associated with hyperhomocysteinemia.[372–377] In a meta-analysis of clinical trials evaluating the efficacy of folate supplementation for stroke prevention, folate was associated with an 18% reduction (RR, 0.82; 95% CI, 0.68 to 1.00; $P=0.045$) in primary stroke risk.[376] Supplementation also appeared to be beneficial for stroke prevention in patients receiving folate for >36 months, cases with ≥20% reduction in homocysteine, and in populations without folate grain supplementation. Despite this, clinical trials focusing on secondary prevention in patients with cardiovascular disease or stroke have failed to demonstrate a benefit for homocysteine-reducing vitamins. The Heart Outcomes Prevention Evaluation (HOPE-2) trial was a randomized, placebo-controlled trial comparing homocysteine-lowering vitamins (2.5 mg of folic acid, 50 mg of vitamin B_6, 2 mg of vitamin B_{12}) or placebo in 5522 patients >55 years of age with vascular disease or diabetes, irrespective of baseline homocysteine.[378] Approximately 12% of the population had a TIA or stroke at study entry. Subjects were followed up for 5 years. The primary outcome was the composite of death due to cardiovascular causes, MI, or stroke. Vitamin therapy did not reduce the risk of the primary end point, but there was a lower risk of stroke (4.0% versus 5.3%; RR, 0.75; 95% CI, 0.59 to 0.97; $P=0.03$) in the active therapy group. The Vitamin Intervention for Stroke Prevention (VISP) study randomly assigned patients with a noncardioembolic stroke and mild to moderate hyperhomocysteinemia (>9.5 μmol/L for men and ≥8.5 μmol/L for women) to receive either a high- or low-dose vitamin therapy (e.g. folate, B_6, or B_{12}) for 2 years.[379] The risk of stroke was related to level of homocysteine; the mean reduction in homocysteine was greater in the high-dose group, but there was no reduction in stroke rates in patients treated with the high-dose vitamins. Two-year stroke rates were 9.2% in the high-dose and 8.8% in the low-dose arms. At present there is no proven clinical benefit for high-dose vitamin therapy for mild to moderate hyperhomocysteinemia.

Recommendation

1. Although folate supplementation reduces levels of homocysteine and may be considered for patients with ischemic stroke and hyperhomocysteinemia *(Class IIb; Level of Evidence B)*, there is no evidence that reducing homocysteine levels prevents stroke recurrence (Table 10).

D. Hypercoagulable States

Inherited Thrombophilias

Little is known about the effect of inherited thrombophilias on the risk of recurrent stroke after stroke or TIA. Studies reported in the literature have been limited to case reports, case series, and small case-control studies in patients with initial stroke. There are inconsistent data on the relative risk associated with a homozygous, as opposed to heterozygous, state and the subsequent risk of stroke. This is likely a result of heterogeneity in the patient populations and varied outcome definitions. No clinical stroke trial has compared the efficacy of different antithrombotic approaches based on genotype.

Inherited thrombophilias (eg, protein C, protein S, or antithrombin III deficiency; factor V Leiden; or the prothrombin G20210A mutation), and the methylenetetrahydrofolate reductase (MTHFR) C677T mutation rarely contribute to adult stroke but may play a larger role in pediatric stroke.[380,381] The most prevalent inherited coagulation disorder is activated protein C (APC) resistance, caused by a mutation in factor V (most commonly the factor V Leiden mutation, Arg506Gln). More commonly a cause of venous thromboembolism, APC resistance has been linked to ischemic stroke in case reports.[382–385] The link between APC resistance and arterial stroke is tenuous in adult stroke but may be more significant in pediatric stroke.[225,386] Both the factor V Leiden (FVL) and the G20210A polymorphism in the prothrombin gene (PT G20210A) have been similarly linked to venous thrombosis, but their role in ischemic stroke remains controversial.[377,387–389]

Studies in younger patients (<55 years of age) have shown an association between these prothrombotic genetic variants and ischemic stroke, but this association remains controversial in an older population with vascular risk factors and competing high-risk stroke mechanisms. Even in the young, results have been inconsistent. In a small study of cryptogenic stroke patients <50 years of age, there was an increased risk (OR, 3.75; 95% CI, 1.05 to 13.34) associated with the PT G20210A mutation, but no significant association with FVL.[389] In contrast, 2 other studies of young (<50 years) patients found no association between ischemic stroke and the FVL, PT G20210A, or the MTHFR C677T mutations.[377,390] Genetic factors associated with venous thrombo-

375. Clarke R, Daly L, Robinson K, Naughten E, Cahalane S, Fowler B, Graham I. Hyperhomocysteinemia: an independent risk factor for vascular disease. *N Engl J Med*. 1991;324:1149–1155.
376. Boushey CJ, Beresford SA, Omenn GS, Motulsky AG. A quantitative assessment of plasma homocysteine as a risk factor for vascular disease: probable benefits of increasing folic acid intakes. *JAMA*. 1995;274:1049–1057.
377. Madonna P, de Stefano V, Coppola A, Casillo F, Carbone AM, Orefice G, Di Minno G. Hyperhomocysteinemia and other inherited prothrombotic conditions in young adults with a history of ischemic stroke. *Stroke*. 2002;33:51–56.
378. Wang X, Qin X, Demirtas H, Li J, Mao G, Huo Y, Sun N, Liu L, Xu X. Efficacy of folic acid supplementation in stroke prevention: a meta-analysis. *Lancet*. 2007;369:1876–1882.
379. Lonn E, Yusuf S, Arnold MJ, Sheridan P, Pogue J, Micks M, McQueen MJ, Probstfield J, Fodor G, Held C, Genest J Jr. Homocysteine lowering with folic acid and B vitamins in vascular disease. *N Engl J Med*. 2006;354:1567–1577.
380. Toole JF, Malinow MR, Chambless LE, Spence JD, Pettigrew LC, Howard VJ, Sides EG, Wang CH, Stampfer M. Lowering homocysteine in patients with ischemic stroke to prevent recurrent stroke, myocardial infarction, and death: the Vitamin Intervention for Stroke Prevention (VISP) randomized controlled trial. *JAMA*. 2004;291:565–575.
381. Hankey GJ, Eikelboom JW, van Bockxmeer FM, Lofthouse E, Staples N, Baker RI. Inherited thrombophilia in ischemic stroke and its pathogenic subtypes. *Stroke*. 2001;32:1793–1799.
382. Ganesan V, McShane MA, Liesner R, Cockson J, Hann I, Kirkham FJ. Inherited prothrombotic states and ischaemic stroke in childhood. *J Neurol Neurosurg Psychiatry*. 1998;65:508–511.
383. Koster T, Rosendaal FR, de Ronde H, Briet E, Vandenbroucke JP, Bertina RM. Venous thrombosis due to poor anticoagulant response to activated protein C: Leiden Thrombophilia Study. *Lancet*. 1993;342:1503–1506.
384. Svensson PJ, Dahlbäck B. Resistance to activated protein C as a basis for venous thrombosis. *N Engl J Med*. 1994;330:517–522.
385. Lindblad B, Svensson PJ, Dahlbäck B. Arterial and venous thromboembolism with fatal outcome and resistance to activated protein C. *Lancet*. 1994;343:917.
386. Simioni P, de Ronde H, Prandoni P, Saladini M, Bertina RM, Girolami A. Ischemic stroke in young patients with activated protein C resistance: a report of three cases belonging to three different kindreds. *Stroke*. 1995;26:885–890.
387. Poort SR, Rosendaal FR, Reitsma PH, Bertina RM. A common genetic variation in the 3'-untranslated region of the prothrombin gene is associated with elevated plasma prothrombin levels and an increase in venous thrombosis. *Blood*. 1996;88:3698–3703.
388. Bertina RM, Koeleman BP, Koster T, Rosendaal FR, Dirven RJ, de Ronde H, van der Velden PA, Reitsma PH. Mutation in blood coagulation factor V associated with resistance to activated protein C. *Nature*. 1994;369:64–67.
389. Ridker PM, Hennekens CH, Lindpaintner K, Stampfer MJ, Eisenberg PR, Miletich JP. Mutation in the gene coding for coagulation factor V and the risk of myocardial infarction, stroke, and venous thrombosis in apparently healthy men. *N Engl J Med*. 1995;332:912–917.
390. Martinelli I, Franchi F, Akhavan S, Bettini P, Morabi G, Mannucci PM. The transition G to A at position 20210 in the 3'-untranslated region of the prothrombin gene is not associated with cerebral ischemia. *Blood*. 1997;90:3806.
391. Longstreth WT Jr, Rosendaal FR, Siscovick DS, Vos HL, Schwartz SM, Psaty BM, Raghunathan TE, Koepsell TD, Reitsma PH. Risk of stroke in young women and two prothrombotic mutations: factor V Leiden and prothrombin gene variant (G20210A). *Stroke*. 1998;29:577–580.
392. Ridker PM, Hennekens CH, Miletich JP. G20210A mutation in prothrombin gene and risk of myocardial infarction, stroke, and venous thrombosis in a large cohort of US men. *Circulation*. 1999;99:999–1004.
393. De Stefano V, Chiusolo P, Paciaroni K, Casorelli I, Rossi E, Molinari M, Servidei S, Tonali PA, Leone G. Prothrombin G20210A mutant genotype is a risk factor for cerebrovascular ischemic disease in young patients. *Blood*. 1998;91:3562–3565.
394. Margaglione M, D'Andrea G, Giuliani N, Brancaccio V, De Lucia D, Grandone E, De Stefano V, Tonali PA, Di Minno G. Inherited prothrombotic conditions and premature ischemic stroke: sex difference in the association with factor V Leiden. *Arterioscler Thromb Vasc Biol*. 1999;19:1751–1756.
395. Voetsch B, Damasceno BP, Camargo EC, Massaro A, Bacheschi LA, Scaff M, Annichino-Bizzacchi JM, Arruda VR. Inherited thrombophilia as a risk factor for the development of ischemic stroke in young adults. *Thromb Haemost*. 2000;83:229–233.
396. Khairy P, O'Donnell CP, Landzberg MJ. Transcatheter closure versus medical therapy of patent foramen ovale and presumed paradoxical thromboembolism: a systematic review. *Ann Intern Med*. 2003;139:753–760.
397. Pezzini A, Del Zotto E, Magoni M, Costa A, Archetti S, Grassi M, Akkawi NM, Albertini A, Assanelli D, Vignolo LA, Padovani A. Inherited thrombophilic disorders in young adults with ischemic stroke and patent foramen ovale. *Stroke*. 2003;34:28–33.
398. Juul K, Tybjaerg-Hansen A, Steffensen R, Kofoed S, Jensen G, Nordestgaard BG. Factor V Leiden: the Copenhagen City Heart Study and 2 meta-analyses. *Blood*. 2002;100:3–10.
399. Aznar J, Mira Y, Vaya A, Cocella D, Ferrando F, Villa P, Estelles A. Factor V Leiden and prothrombin G20210A mutations in young adults with cryptogenic ischemic stroke. *Thromb Haemost*. 2004;91:1081–1084.
400. Lopaciuk S, Bykowska K, Kwiecinski H, Gladkiewicz A, Czlonkowska A, Mandel T, Kuczynska-Zardzewialy A, Szalagowska D, Windyga J, Schroder W, Hermann FH, Jedrzejowska H. Factor V Leiden, prothrombin gene G20210A variant, and methylenetetrahydrofolate reductase C677T genotype in young adults with ischemic stroke. *Clin Appl Thromb Hemost*. 2001;7:346–350.
401. Casas JP, Hingorani AD, Bautista LE, Sharma P. Meta-analysis of genetic studies in ischemic stroke: thirty-two genes involving approximately 18,000 cases and 58,000 controls. *Arch Neurol*. 2004;61:1652–1661.
402. Kim RJ, Becker RC. Association between factor V Leiden, prothrombin G20210A, and methylenetetrahydrofolate reductase C677T mutations and events of the arterial circulatory system: a meta-analysis of published studies. *Am Heart J*. 2003;146:948–957.
403. Hyers TM, Agnelli G, Hull RD, Morris TA, Samama M, Tapson V, Weg JG. Antithrombotic therapy for venous thromboembolic disease. *Chest*. 2001;119(suppl 1):176S–193S.
404. Ridker PM, Goldhaber SZ, Danielson E, Rosenberg Y, Eby CS, Deitcher SR, Cushman M, Moll S, Kessler CM, Elliott CG, Paulson R, Wong T, Bauer KA, Schwartz BA, Miletich JP, Baumgartner H, Glynn RJ. Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism. *N Engl J Med*. 2003;348:1425–1434.
405. Warkentin TE, Greinacher A. Heparin-induced thrombocytopenia: recognition, treatment, and prevention: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*. 2004;126(suppl 3):311S–337S.
406. Levi M, de Jonge E, van der Poll T, ten Cate H. Novel approaches to the management of disseminated intravascular coagulation. *Crit Care Med*. 2000;28(suppl 9):S20–S24.
407. Kakkar AK, Williamson RC. Thromboprophylaxis in the cancer patient. *Haemostasis*. 1998;28(suppl 3):61–65.
408. Monreal M, Zacharski L, Jimenez JA, Roncales J, Villaseca B. Fixed-dose low-molecular-weight heparin for secondary prevention of venous thromboembolism in patients with disseminated cancer: a prospective cohort study. *J Thromb Haemost*. 2004;2:1311–1315.
409. Vila P, Hernandez MC, Lopez-Fernandez MF, Batlle J. Prevalence, follow-up and clinical significance of the anticardiolipin antibodies in normal subjects. *Thromb Haemost*. 1994;72:209–213.
410. Cervera R, Font J, Gomez-Puerta JA, Espinosa G, Ordi-Ros J, Ramos-Casals M, Ingelmo M; Hospital Clinic Antiphospholipid Syndrome Registry Project Group. Validation of the preliminary criteria for the classification of catastrophic antiphospholipid syndrome. *Ann Rheum Dis*. 2005;64:1205–1209.
411. Wilson WA, Gharavi AE, Koike T, Lockshin MD, Branch DW, Piette JC, Brey R, Derksen R, Harris EN, Hughes GR, Triplett DA, Khamashta MA. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an international workshop. *Arthritis Rheum*. 1999;42:1309–1311.
412. Bladon A, Guegan-Massardier E, Thiquenot A, Onnient Y, Thon F, Boog JY, Mahout B. Antiphospholipid antibodies in the acute phase of cerebral ischemia in young adults: a descriptive study of 139 patients. *Cerebrovasc Dis*. 2002;13:156–162.
413. Nencini P, Baruffi MC, Abbate R, Massai G, Amaducci L, Inzitari D. Lupus anticoagulant and anticardiolipin antibodies in young adults with cerebral ischemia. *Stroke*. 1992;23:189–193.