ACUTE STROKE
Supporting information

This guideline has been prepared with reference to the following:

NICE. Cardiovascular disease: risk assessment and reduction, including lipid modification. 2023. NICE. London

https://www.nice.org.uk/guidance/ng238

NICE. Stroke: Stroke and transient ischaemic attack in over 16s: diagnosis and initial management. 2022. NICE. London

https://www.nice.org.uk/guidance/ng128

NICE. Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation. 2021. NICE. London

https://www.nice.org.uk/guidance/ta249

NICE. Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation. 2021. NICE. London

https://www.nice.org.uk/guidance/ta256

NICE. Apixaban for preventing stroke and systemic embolism in people with nonvalvular atrial fibrillation. 2021. NICE. London

http://www.nice.org.uk/guidance/ta275

NICE. Therapeutic hypothermia for acute ischaemic stroke. 2019. NICE. London

https://www.nice.org.uk/guidance/ipg647

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. Stroke. 2018;49:e46-e110

https://www.ahajournals.org/doi/10.1161/STR.0000000000000158

NICE. Mechanical clot retrieval for treating acute ischaemic stroke. 2016. NICE. London

https://www.nice.org.uk/guidance/ipg548

Parry-Jones A. Cutting delays in reversing anticoagulation after intracerebral haemorrhage: three key changes at a UK comprehensive stroke centre. BMJ Qual Improv Rep. 2015;4

http://qir.bmj.com/content/4/1/u208763.w3521

Huhtakangas J, Tetri S, Juvela S et al. Improved survival of patients with warfarin-associated intracerebral haemorrhage: a retrospective longitudinal population-based study. Int J Stroke. 2015;10: 876-81

Kuramatsu JB, Gerner ST, Schellinger PD et al. Anticoagulant reversal, blood pressure levels, and anticoagulant resumption in patients with anticoagulation-related intracerebral hemorrhage. JAMA. 2015;313:824-36

Patients presenting less than 4.5 hours from symptom onset in ischaemic stroke should be considered for thrombolysis?
A 2015 systematic review found that "intravenous thrombolysis is the mainstay of acute ischemic stroke management for any patient with disabling deficits presenting within 4.5 hours from symptom onset. Randomized trials have demonstrated that more patients return to having good function (defined by being independent and having slight disability or less) when treated within 4.5 hours after symptom onset with intravenous recombinant tissue plasminogen activator (IV rtPA) therapy."
A 2019 RCT concluded that in patients who have ischemic but not yet infarcted brain tissue, the treatment window may be extended to 9 hours. 225 patients were randomly assigned to receive intravenous alteplase or placebo between 4.5 and 9.0 hours after the onset of stroke. The primary outcome was a score of 0 or 1 on the modified Rankin scale, on which scores range from 0 (no symptoms) to 6 (death), at 90 days. The primary outcome occurred in 40 patients (35.4%) in the alteplase group and in 33 patients (29.5%) in the placebo group (adjusted risk ratio, 1.44; 95% confidence interval [CI], 1.01 to 2.06; P = 0.04). Symptomatic intracerebral hemorrhage occurred in 7 patients (6.2%) in the alteplase group and in 1 patient (0.9%) in the placebo group (adjusted risk ratio, 7.22; 95% CI, 0.97 to 53.5; P = 0.05).
A 2024 systematic review found that patients treated with IV thrombolysis within the extended therapeutic window (ETW) of 4.5 up to 24 h since symptom inset had higher rates of favourable outcomes than those who did not receive thrombolytic therapy (Al-Janabi, 2024). These favourable outcomes were observed despite an increase in the rate of symptomatic intracranial hemorrhage among patients treated with thrombolysis in the ETW, and there was no difference in mortality.

Al-Janabi OM, Jazayeri SB, Toruno MA et al. Safety and efficacy of intravenous thrombolytic therapy in the extended window up to 24 hours: A systematic review and meta-analysis. Ann Clin Transl Neurol. 2024;11:3310-9
https://onlinelibrary.wiley.com/doi/10.1002/acn3.52239

Ma H, Campbell BCV, Parsons MW et al. Thrombolysis Guided by Perfusion Imaging up to 9 Hours after Onset of Stroke. N Engl J Med. 2019;380:1795-803

Prabhakaran S, Ruff I, Bernstein RA. Acute stroke intervention: a systematic review. JAMA. 2015;313:1451-62

Evidence Level: I

Aspirin 300 mg improves the outcome in ischaemic stroke?
This is recommended in the 2022 NICE guidelines and is based on the evidence detailed in the question on aspirin under Subsequent Management (see below).

Evidence Level: II

Blood glucose > 11 mmol/l indicates poor prognosis and should be reduced with insulin?
A 2023 systematic review found that the stress hyperglycemia ratio (SHR) exhibited a significant association with the risk of various adverse outcomes (Huang 2023). Specifically, a higher SHR was correlated with a 2.64-fold increased risk of 3-month poor functional outcomes (OR: 2.64, 95% CI 2.05 to 3.41), a 3.11-fold increased risk of 3-month mortality (OR: 3.11, 95% CI 2.10 to 4.59), a 2.80-fold increased risk of 1-year mortality (OR: 2.80, 95% CI 1.81 to 4.31), a 3.90-fold increased risk of intracerebral hemorrhage (ICH) and 4.57-fold increased risk of symptomatic ICH (sICH) (ICH-OR: 3.90, 95% CI 1.52 to 10.02; sICH-OR: 4.57, 95% CI 2.05 to 10.10), a 1.73-fold increased risk of neurological deficits (OR: 1.73, 95 CI 1.44 to 2.08), and a 2.84-fold increased risk of stroke recurrence (OR: 2.84, 95 CI 1.48 to 5.45).
A systematic review and meta-analysis of 26 cohort studies (Capes, 2001) found that the relative risk for in-hospital or 30-day mortality in stroke patients with admission glucose level >6-8 mmol/L was 3.07 (95% CI 2.50-3.79) in non-diabetics and 1.30 (95% CI 0.49-3.43) in diabetics.
A 2020 systematic review concluded that tight glucose control with insulin therapy after acute ischemic stroke is not associated with improvements in mortality, independence, or mRS score and leads to higher rates of symptomatic or severe hypoglycaemia (Cerecedo-Lopez, 2020). A meta-analysis of Twelve RCTs including 2734 patients found that when compared with conventional therapy or placebo, tight glycemic control was associated with similar rates of mortality at ≥90 days follow-up (pooled odds ratio [pOR], 0.99; 95% confidence interval [CI], 0.79 to 1.22]) and independence at ≥90 days follow-up (pOR, 0.95; 95% CI, 0.79 to 1.14). In contrast, tight glycemic

control was associated with increased rates of symptomatic or severe hypoglycemia during treatment (pOR, 5.2; 95% CI, 1.7 to 15.9).

Capes SE, Hunt D, Malmberg K, et al. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview. Stroke 2001;32:2426-32
http://stroke.ahajournals.org/content/32/10/2426.long

Cerecedo-Lopez CD, Cantu-Aldana A, Patel NJ et al. Insulin in the Management of Acute Ischemic Stroke: A Systematic Review and Meta-Analysis. World Neurosurg . 2020;136:e514-e534

Huang YW, Li ZP, Yin XS et al. Stress hyperglycemia and risk of adverse outcomes in patients with acute ischemic stroke: a systematic review and dose–response meta–analysis of cohort studies. Front Neurol. 2023;14:1219863
https://pmc.ncbi.nlm.nih.gov/articles/PMC10701542/

Evidence Level: I

Hypotension indicates poor prognosis and needs correction?
Data from 8,672 patients in the International Stroke Trial (IST) suggested a U-shaped relationship between blood pressure and adverse events. Death within 14 days was more frequent in patients with blood pressure in the highest (10.4% of 2,392 with baseline systolic blood pressure (BSP) >= 180) and lowest (12.4% of 1,603 with baseline BSP < 140) quartiles (Phillips, 1995). The odds of death within 14 days increased by a factor of 1.15 for every 10 mmHg below 150 (Signorini, 1999). These results were replicated in a larger study of 17,398 patients from the IST (Leonardi-Bee, 2002).
A study in 1,455 patients (Aslanyan, 2003) failed to demonstrate greater mortality in patients experiencing a decrease of >30% in baseline mean arterial blood pressure over the first 2.5 days, although an increase of >30% over the same period was associated with greater mortality.
A study in 304 patients (Castillo, 2004) appeared to confirm the U shaped curve: for every 10 mmHg </= 180 mmHg of systolic blood pressure, the risk of early neurological deterioration, poor outcome, and mortality increased by 6%, 25% and 7%, respectively. For every 10 mmHg >180 mmHg, the risk of early neurological deterioration increased by 40% and poor outcome by 23%. There was no effect on mortality.

Aslanyan S, Fazekas F, Weir CJ, et al. Effect of blood pressure during the acute period of ischemic stroke on stroke outcome: a tertiary analysis of the GAIN International Trial. Stroke 2003;34:2420-5
http://stroke.ahajournals.org/content/34/10/2420.long

Castillo J, Leira R, Garcia MM, et al. Blood pressure decrease during the acute phase of ischemic stroke is associated with brain injury and poor stroke outcome. Stroke 2004;35:520-6
http://stroke.ahajournals.org/content/35/2/520.long

Leonardi-Bee J, Bath PM, Phillips SJ, et al. Blood pressure and clinical outcomes in the International Stroke Trial. Stroke 2002;33:1315-20
http://stroke.ahajournals.org/content/33/5/1315.long

Phillips SJ, Sandercock P, Slattery J. U-shaped relationship between systolic blood pressure and early death after acute ischemic stroke. Can J Neurol Sci 1995;22(Suppl 1):S44

Rordorf G, Cramer SC, Efird JT, et al. Pharmacological elevation of blood pressure in acute stroke: clinical effects and safety. Stroke 1997;28:2133-8
http://stroke.ahajournals.org/content/28/11/2133.long

Rordorf G, Koroshetz WJ, Ezzeddine MA, et al. A pilot study of drug-induced hypertension for treatment of acute stroke. Neurology 2001;56:1210-13

Signorini DF, Sandercock PA, Warlow CP. Systolic blood pressure on randomisation and outcome in the International Stroke Trial. Cerebrovasc Dis 1999;9(Suppl 1):34

Evidence Level: III

Blood pressure should not be reduced unless > 220/120 mmHg and there is other evidence of hypertensive encephalopathy?
American Heart Association guidelines (Jauch, 2013) recommend that hypertension in stroke patients should not be treated unless systolic BP exceeds 220 mm Hg or diastolic BP exceeds 120 mm Hg.

2021 guidance from the European Stroke Organisation makes the same recommendation (Sandset, 2021).
The argument for not reducing blood pressure (for up to 10-14 days following the stroke) is that decreasing brain perfusion may produce watershed infarction and encourage thrombus formation (Pushpangadan, 1999).
Two Cochrane systematic reviews (Bath, 2014; Geeganage 2010) looking at data from 26 trials in 17011 patients and 43 trials involving 7649 patients respectively, have concluded that insufficient evidence exists with which to evaluate the effect of altering blood pressure on outcomes in stroke.
An observational study in 372 patients (Vicek, 2003) found that a diastolic blood pressure decrease of >25% in the 24 hours following admission was associated with increased risk for poor neurologic outcome (Rankin Scale score 3-5) on day 5 (RR 3.8; 95% CI 1.2-12.1).

Jauch EC, Saver JL, G, Adams HP, et al. Guidelines for the early management of patients with ischemic stroke: 2007 Guidelines update. A scientific statement from the Stroke Council of the American Heart Association / American Stroke Association. Stroke 2013;44:870-974
http://stroke.ahajournals.org/content/44/3/870.long

Bath PM, Krishnan K. Interventions for deliberately altering blood pressure in acute stroke. Cochrane Database Syst Rev. 2014, No.: CD000039
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000039.pub3/pdf/standard

Geeganage C, Bath PM. Vasoactive drugs for acute stroke. Cochrane Database Syst Rev. 2010, Issue 7. Art. No.: CD002839
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002839.pub2/full

Pushpangadan M, Wright J, Young J. Evidence-based guidelines for early stroke management. Hosp Med 1999;60:105-14

Sandset EC, Anderson CS, Bath PM et al. European Stroke Organisation (ESO) guidelines on blood pressure management in acute ischaemic stroke and intracerebral haemorrhage. Eur Stroke J. 2021;6:XLVIII–LXXXIX
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8370078/

Vicek M, Schillinger M, Lang W, et al. Association between course of blood pressure within the first 24 hours and functional recovery after acute ischemic stroke. Ann Emerg Med 2003;42:619-26

Evidence Level: I

In patients with intracranial haemorrhage GTN infusion and/or labetalol should be used to lower blood pressure rapidly (within 1 hr)?
2021 guidance from the European Stroke Organisation states that “In patients with acute intracerebral haemorrhage, we suggest initiating antihypertensive treatment as early as possible and ideally within 2 hours of symptom onset. The decrease of systolic blood pressure should not exceed 90mmHg from baseline values” (Sandset, 2021).
In the INTERACT2 randomised controlled trial (Anderson 2013) a total of 2839 participants (mean age, 63.5 years; 62.9% men) were enrolled at 144 hospitals in 21 countries; 1403 participants were randomly assigned to receive early intensive treatment to lower their blood pressure, and 1436 were assigned to receive American Heart Association/American Stroke Association guideline-recommended treatment (Morgensterm 2010). The study found that early intensive lowering of blood pressure did not result in a significant reduction in the rate of the primary outcome of death or major disability, but an ordinal analysis of scores on the modified Rankin scale did suggest that intensive treatment improved functional outcomes.
A 2024 review stated that the optimal agent or class of drugs to control blood pressure is not known and has not been well explored in trials (Mutimer, 2024).

Anderson CS, Heeley E, Huang Y et al. Rapid Blood-Pressure Lowering in Patients with Acute Intracerebral Hemorrhage. N Engl J Med 2013; 368:2355-2365
http://www.nejm.org/doi/full/10.1056/NEJMoa1214609#t=articleTop

Mutimer CA, Yassi N, Wu TY. Blood Pressure Management in Intracerebral Haemorrhage: when, how much, and for how long? Curr Neurol Neurosci Rep. 2024;24:181–9
https://pmc.ncbi.nlm.nih.gov/articles/PMC11199276/

Sandset EC, Anderson CS, Bath PM et al. European Stroke Organisation (ESO) guidelines on blood pressure management in acute ischaemic stroke and intracerebral haemorrhage. Eur Stroke J. 2021;6:XLVIII–LXXXIX https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8370078/

Evidence Level: I

Hemicraniectomy reduces mortality in patients with MCA syndrome?
Three European randomised trials (DECIMAL, DESTINY, HAMLET) in a total of 93 patients found that, after data was pooled, more patients in the decompressive surgery group (compared to controls) had a modified Rankin scale (mRS) score </= 4 (75% vs 29%; pooled absolute RR 51%; 95% CI 34-69). Decompressive surgery also resulted in more patients with a mRS </= 3 (43% vs 21%; 23% [5-41]) and better survival (78% vs 29%; 50% [33-67]). NNT for survival with mRS </= 4 was 2; for survival with mRS </= 3 was 4; for survival irrespective of functional outcome was 2 (Vahedi, 2007). Previous trials had only explored patients <60 years old (only 50% of patients actually affected by MCA). The DESTINY 2 trial sought to address this. Patients 61 or older with malignant cerebral artery were randomised to receive either conservative treatment in intensive care or hemicraniectomy (within 48 h of onset). The trial found that the surgery increased survival rate without serious disability. The majority of survivors required assistance with most bodily needs (Juttler, 2014).

Juttler E, Unterberg A, Woitzik J et al. Hemicraniectomy in Older Patients with Extensive Middle-Cerebral-Artery Stroke. N Engl J Med 2014; 370:1091-100
http://www.nejm.org/doi/full/10.1056/NEJMoa1311367

Vahedi K, Hofmeijer J, Juettler E, et al. Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomised controlled trials. Lancet Neurol 2007;6:215-22

Evidence level: I

Patients' joints should be mobilised through their natural range of movement 4 times a day?
A randomised trial in 223 patients (Cuesy, 2010) found that the incidence of nosocomial pneumonia (NP) was reduced in the group (n=111) given joint mobilisation (the "turn-mob program") by previously trained relatives, as compared to a control group (n=112) who received standard care (turning by nursing staff). Fourteen (12.6%) of the "turn-mob" group developed NP, vs 30 (26.8%) of the control group (RR 0.39, 95% CI .19 - .79; P = .008).

Cuesy PG, Sotomayor PL, Pina JO. Reduction in the incidence of poststroke nosocomial pneumonia by using the "turn-mob" program. J Stroke Cerebrovasc Dis 2010;19:23-8

Evidence Level: II

Patients with prosthetic valves and disabling cerebral infarct and at high risk of haemorrhagic transformation should have warfarin stopped for one week and replaced with aspirin 300 mg once daily?
This advice is taken directly from the 2022 NICE guideline (see top of page). No supporting evidence for this is offered by NICE.

Evidence Level: V

Subsequent Management

Aspirin 300 mg daily reduces the risk of a further stroke?
Evidence from a Cochrane Review (Sandercock, 2014) indicates that aspirin (160-300 mg daily), started within 48 hours of onset of ischaemic stroke, prevents around 1 death or non-fatal recurrent stroke for every 100 patients treated for the next 2-4 weeks.
A critical review and meta-analysis (Owen, 2010) suggested that the belief that aspirin at doses of 75 to 325 mg daily was an effective treatment was based on a flawed interpretation of the data. A Bayesian network meta analysis demonstrated that aspirin at 325 mg daily was superior to control and similar to warfarin for the reduction of the risk of both stroke and death. In contrast for lower daily doses of aspirin there was no evidence of any efficacy over control for the reduction of the risk of stroke. The data were inconclusive as to whether lower doses of aspirin may have some benefit in reducing the risk of death.

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Sandercock P, Counsell C, Tseng M et al. Oral antiplatelet therapy for acute ischaemic stroke. Cochrane Database Syst Rev. 2014, Art. No.: CD000029
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000029.pub3/full

Owen A. Antithrombotic treatment for the primary prevention of stroke in patients with non valvular atrial fibrillation: a reappraisal of the evidence and network meta analysis. Int J Cardiol 2010;142:218-23

Evidence Level: II

Is there evidence for routine use of heparin/dalteparin following stroke?
A systematic review (Geenganage 2012) of 15 trials of low dose subcutaneous anticoagulation found that low-dose heparin increased symptomatic intracerebral haemorrhage by more than they reduced symptomatic pulmonary embolism in patients with recent ischemic stroke. Therefore, their routine acute use cannot be recommended. They may still be relevant in patients at very high risk of PE (e.g, morbid obesity, previous venous thromboembolism, and inherited thrombophilia).
A 2020 systematic review concluded that we should be cautious about using low molecular weight heparin (LMWH) in acute stroke patients aged older than 70 years because it may increase the risk of all-cause mortality (Ye, 2020). For patients younger than 70 years old, the early use of LMWH significantly reduces the short-term risk of DVT, but there is no significant relationship in the long term. In terms of DVT prevention, enoxaparin and danaparoid are probably more effective. According to age-stratified analyses, the risk of all-cause mortality increased by 39% (risk ratio 1.39, 1.03 to 1.88) in acute stroke patients aged older than 70 years who used LMWH for 14 days, and there was no significant effect on preventing DVT (risk ratio 0.69, 0.14-3.52) in patients aged younger than 70 years old within 3 months.

Geeganage CM, Sprigg N, Bath MW et al. Balance of symptomatic pulmonary embolism and symptomatic intracerebral hemorrhage with low-dose anticoagulation in recent ischemic stroke: a systematic review and meta-analysis of randomized controlled trials. J Stroke Cerebrovasc Dis. 2013;22:1018-27

Ye Y, Zhou W, Cheng W et al. Short-Term and Long-Term Safety and Efficacy of Treatment of Acute Ischemic Stroke with Low-Molecular-Weight Heparin: Meta-Analysis of 19 Randomized Controlled Trials. World Neurosurg. 2020;141:e26-e41

Evidence Level: I

There is no need to avoid proton pump inhibitors (PPIs) in patients taking clopidogrel following stroke?
A nested case control study (Juurlink, 2010) compared 118 patients re-admitted for stroke with 472 controls. After multivariable adjustment, current use of proton pump inhibitors was not associated with a significantly increased risk of recurrent stroke (adjusted odds ratio, 1.05; 95% CI, 0.60 to 1.82) or death (adjusted odds ratio, 1.84; 95% CI, 0.88 to 3.89).
A 2023 South Korean retrospective cohort study found that the prescription of PPIs in addition to clopidogrel was associated with an increased risk of recurrent stroke (Lee, 2023). There was a higher incidence of recurrent stroke in the PPI co-prescription group (PPI co-prescription group (n = 373) vs. non-prescription group (n = 1051); 81/240 person years vs. 189/740 person years, hazard ratio: 1.34, 95% CI; 1.01 to 1.76, p = 0.04).

Juurlink DN, Gomes T, Mamdani MM, et al. The safety of proton pump inhibitors and clopidogrel in patients after stroke. Stroke 2011 42:128-32
http://stroke.ahajournals.org/content/42/1/128.long

Lee YK, Lim HS, Choi YI et al. Impact of Concomitant Use of Proton Pump Inhibitors and Clopidogrel on Recurrent Stroke and Myocardial Infarction. Pharmaceuticals (Basel). 2023;16:1213
https://pmc.ncbi.nlm.nih.gov/articles/PMC10535402/

Evidence Level: III

Carotid ultrasound is indicated for patients who have had a carotid territory ischaemic event (TIA/minor infarct), who have made a good recovery and who are surgical candidates?
The risks of carotid endarterectomy are increased by the presence of diffuse carotid artery stenosis, so accurate diagnosis is essential before surgery (Rothwell, 1997). Analysis of data from 1,729

patients (Rothwell, 1997) shows the risk of stroke and death is increased in stenosis of the distal ipsilateral internal carotid artery (OR 1.56, 95% CI 1.03 – 2.36) or of the ipsilateral external carotid artery (OR 1.61, 95% CI 1.05 – 2.47). In a review of 120 carotid vessels, in 60 patients (White, 1994), Doppler ultrasonography yielded a sensitivity of 88% and a specificity of 81%, equivalent to magnetic resonance angiography (84% and 81%). Carotid duplex ultrasonography is equally accurate (Blakeley, 1995).

Blakeley DD, Oddone EZ, Hasselblad V, et al. Noninvasive carotid artery testing: a meta-analytic review. Ann Intern Med 1995;122:360-7

Rothwell PM, Slattery J, Warlow CP. Clinical and angiographic predictors of stroke and death from carotid endarterectomy: systematic review. BMJ 1997;315:1571-7
http://www.bmj.com/content/315/7122/1571.long

White JE, Russell WL, Greer MS, et al. Efficacy of screening MR angiography and Doppler ultrasonography in the evaluation of carotid artery stenosis. Am Surg 1994;60:340-8

Evidence Level: III

Echocardiography is indicated for patients <50 years or who have murmurs and/or a history of rheumatic fever? Do these patients have a high risk of arteritis and thrombotic disorders? Does an intracerebral bleed indicate an operable vascular abnormality?
Transthoracic echocardiography finds relevant lesions in only 25% of patients > 45 years; in patients < 45 years, this rises to 54% (Beattie, 1998). A study in 40 patients, comparing transthoracic (TTE) with transesophageal (TEE) echocardiography, found that TEE picked up pathologic findings in 9 of 20 patients (45%) with normal TTE readings (Zenker, 1988). TEE is not indicated in all patients, but may be useful in those in whom carotid stenoses have been excluded (Channon, 1999).
In a study of 329 ischaemic stroke patients aged 15 to 45 (Adams, 1995), 27 cases (8.2%) were due to small-artery occlusion and 19 (5.8%) to haematologic disorders. Findings were similar in 3,362 consecutive patients from the Lausanne Stroke Registry (Baptista, 1999): 8.3% due to arteritis and 6.7% to haematologic conditions.
Patients with arteriovenous malformations in the brain have an annual risk of haemorrhage of 2-4% (Kondziolka, 1995).

Adams HP, Kappelle LJ, Biller J, et al. Ischemic stroke in young adults: experience in 329 patients enrolled in the Iowa Registry of Stroke in Young Adults. Arch Neurol 1995;52:491-5

Baptista MV, van Melle G, Bogousslavsky J. Prediction of in-hospital mortality after first-ever stroke: the Lausanne Stroke Registry. J Neurol Sci 1999;166:107-14

Beattie JR, Cohen DJ, Manning WJ, et al. Role of routine transthoracic echocardiography in evaluation and management of stroke. J Intern Med 1998;243-91
http://onlinelibrary.wiley.com/doi/10.1046/j.1365-2796.1998.00300.x/epdf

Channon KM, Banning AP. Echocardiography in stroke and thromboembolism: transoesophageal imaging for all? QJM 1999;92:619-21

Kondziolka D, McLaughlin MR, Kestle JR. Simple risk predictions for ateriovenous malformation hemorrhage. Neurosurgery 1995;37:851-5

Zenker G, Erbel R, Kramer G, et al. Transesophageal two-dimensional echocardiography in young patients with cerebral ischemic events. Stroke 1988;19:345-8
http://stroke.ahajournals.org/content/19/3/345.long

Evidence Level: V

Frail, malnourished, multimorbid patients or those on multiple medications should be prescribed anticoagulants according to the OATES regimen?
This regimen (Oates, 1998) was the result of a study in 107 consecutive outpatients (mean age 70 years, range 64-86) in which a range of variables was used to calculate the eventual maintenance dose of warfarin. The INR after 2 weeks of 2 mg warfarin therapy predicted 70% of the variability of the maintenance dose.

Oates A, Jackson PR, Austin CA, et al. A new regimen for starting warfarin therapy in out-patients. Br J Clin Pharmacol 1998;46:157-61
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1873664/pdf/bcp0046-0157.pdf

Further investigations

Young patients with patent foramen ovale/atrial septal defect should be given full thrombophilia screening?

A prospective cohort study of 83 TIA/stroke patients with a patent foramen ovale (PFO) and or inter-atrial septal aneurysm (IASA) found eighteen (21.7%) had ≥1 abnormality on thrombophilia screening (Lim, 2017). The most important abnormalities which led to treatment changes in 11 patients (13.3%) were primary anti-phospholipid syndrome (N=3; 3.6%), protein S deficiency (N=2; 2.4%) hyper-homocysteinaemia (N=6/72 screened, 8.3%). The authors concluded that comprehensive arterial and venous thrombophilia screening is warranted in TIA/ischaemic stroke patients with a PFO and/or IASA.

A review of this subject (Morris, 2010) states that: ”Multiple case-control studies have not convincingly shown an association of the inherited thrombophilias with ischemic stroke, even in young patients and patients with patent foramen ovale. If there is an association between the inherited thrombophilias and arterial stroke, then it is a weak one, likely enhanced by other prothrombotic risk factors. The consequences of ordering these tests and attributing causality to an arterial event can result in significant costs to the health care system and pose a potential risk to patients, because this may lead to inappropriate use of long-term oral anticoagulants, exposing patients to harm without a clearly defined benefit.”

Lim ST, Murphy SJX, Smith DR et al. Clinical outcomes and a high prevalence of abnormalities on comprehensive arterial and venous thrombophilia screening in TIA or ischaemic stroke patients with a patent foramen ovale, an inter-atrial septal aneurysm or both. J Neurol Sci. 2017;377:227-233

Morris JG, Singh S, Fisher M. Testing for inherited thrombophilias in arterial stroke: can it cause more harm than good? Stroke 2010;41:2985-90
http://stroke.ahajournals.org/content/41/12/2985.long

Evidence Level: V

Complications

Stroke patients are at high risk of depression?

A 2019 systematic review of six prospective studies (4648 patients) found that the prevalence of poststroke depression was found to be from 15.9% to 40.5% (Wu, 2019).

A 2023 systematic review of 77 studies found the overall prevalence of depression was 27% (95% CI 25 to 30) [Liu, 2023]. A Prevalence of depression was 24% (95% CI 21 to 28) by clinical interview and 29% (95% CI 25 to 32) by rating scales. Among people who were depressed within 3 months of stroke, 53% (95% CI 47 to 59) experienced persistent depression, while 44% (95% CI 38 to 50) recovered. The incidence of later depression (3 to 12 months after stroke) was 9% (95% CI 7 to 12).

Liu L, Xu M, Marshall IJ et al. Prevalence and natural history of depression after stroke: A systematic review and meta-analysis of observational studies. PLoS Med. 2023;20
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10047522/

Wu QE, Zhou AM, Han YP et al. Poststroke Depression and Risk of Recurrent Stroke: A Meta-Analysis of Prospective Studies. Medicine (Baltimore) 2019;98:e17235

Evidence Level: I

Patients with atrial fibrillation are at high risk of stroke and warfarin reduces this risk?

A 2015 systematic review found that patients with atrial fibrillation had a 5-fold increased risk of stroke (Lip, et al). They also found evidence that vitamin K antagonists such as warfarin can reduce this risk (RR reduction, 64%; 95% CI, 49%-74%).

A Cochrane review (Koudstaal, 2004) of 2 trials involving 485 patients found that oral anticoagulants (target INR = 2.5 – 4.0) reduced the risk of recurrent stroke by two-thirds (OR 0.36, 95% CI 0.22-0.58) in patients with atrial fibrillation. The risk of all vascular events was reduced by almost one half (OR 0.55, 95% CI 0.37-0.82). No intracranial bleeds were reported.

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Lip GY, Lane DA. Stroke prevention in atrial fibrillation: a systematic review. JAMA. 2015;313:1950-62

Koudstaal PJ. Anticoagulants for preventing stroke in patients with nonrheumatic atrial fibrillation and a history of stroke or transient ischemic attacks. Cochrane Database Syst Rev. 2004, Issue 1. Art. No.: CD000185.pub2 http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000185.pub2/full

Evidence Level: I

The risk of stroke is increased in smokers and those with hypertension, diabetes or hyperlipidaemia?

A 2019 systematic review (including 14 observational studies involving 303,134 subjects) found that smokers had an overall increased risk of stroke compared with non-smokers, with a pooled odds ratio (OR) of 1.61 (95% confidence interval [CI]: 1.34 to 1.93, P<.001) [Pan, 2019]. A subgroup analysis conducted based on smoking status revealed ORs of 1.92 (95% CI: 1.49 to 2.48) for current smokers and 1.30 (95% CI: 0.93 to 1.81) for former smokers.

Hyperlipidaemia is strongly associated with mortality from coronary heart disease, but less so with stroke. An overview of 16 randomised trials involving 29,000 patients followed up for an average of 3.3 years (Hebert, 1997) found a 29% reduction in the risk of stroke (95% CI 14%-41%) in those given statins to reduce total cholesterol levels by 22%.

A 2023 systematic review of 12 studies found that diabetes is an independent risk factor for stroke (Mosenzon, 2023). Furthermore, the risk of stroke is higher in people with either type 1 diabetes (HR: 1.50; 95% CI: 1.23 to 1.83) or type 2 diabetes (HR: 1.76; 95% CI: 1.65 to 1.87) compared with people without diabetes. Furthermore, there appear to be differences in the risk of stroke between sexes among people with diabetes, with evidence suggesting a greater risk amongst women than men. In a meta-analysis, the adjusted relative risk of any stroke associated with diabetes was 2.28 (95% CI: 1.93 to 2.69) in women, whereas it was 1.83 (95% CI: 1.60 to 2.08) in men, when compared with individuals without diabetes.

Hypertension is one of the strongest risk factors for stroke in the general population, and the risk of stroke increases linearly when blood pressure levels exceed 115/75 mmHg (Lewington, 2002). Blood pressure variables, such as systolic blood pressure, diastolic blood pressure, and mean arterial pressure, are all associated with an increased risk of stroke (Bangalore, 2009), and lowering of the blood pressure with any antihypertensive agent reduces the risk with as much as 30% (Lawes, 2004).

Bangalore S, Messerli FH, Franklin SS et al. Pulse pressure and risk of cardiovascular outcomes in patients with hypertension and coronary artery disease: an INternational VErapamil SR-trandolapril STudy (INVEST) analysis. Eur Heart J. 2009;30:1395–401

Barrett-Connor E, Khaw KT. Diabetes mellitus: an independent risk factor for stroke? Am J Epidemiol 1988;128:116-23
http://aje.oxfordjournals.org/content/128/1/116.long

Hebert PR, Gaziano JM, Chan KS, et al. Cholesterol lowering with statin drugs, risk of stroke, and total mortality: an overview of randomized trials. JAMA 1997;278:313-21

Lawes CM, Bennett DA, Feigin VL et al. Blood pressure and stroke: an overview of published reviews. Stroke. 2004;35:776–85

Lewington S, Clarke R, Qizilbash N et al. Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002;360:1903–13

Mosenzon O, Cheng AY, Rabinstein AA et al. Diabetes and Stroke: What Are the Connections? J Stroke. 2023; 25:26-38
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9911852/

Pan B, Jin X, Jun L et al. The Relationship Between Smoking and Stroke: A Meta-Analysis. Medicine (Baltimore) 2019;98:e14872
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6708836/

Evidence Level: III

Risks/benefits ratio of carotid endarterectomy acceptable for patients with > 70% stenosis in appropriate carotid artery if shown by Doppler ultrasound?
A 2020 systematic review of RCTs (three trials involving 6343 participants) concluded that carotid endarterectomy reduced the risk of recurrent stroke for people with significant stenosis (Rerkasem, 2020). Endarterectomy might be of some benefit for participants with 50% to 69% symptomatic stenosis and highly beneficial for those with 70% to 99% stenosis. The results of the meta-analysis showed that surgery increased the five-year risk of any stroke or operative death in participants with less than 30% stenosis (risk ratio (RR) 1.25, 95% confidence interval (CI) 0.99 to 1.56) Surgery decreased the five-year risk of any stroke or operative death in participants with 30% to 49% stenosis (RR 0.97, 95% CI 0.79 to 1.19), was of benefit in participants with 50% to 69% stenosis (RR 0.77, 95% CI 0.63 to 0.94), and was highly beneficial in participants with 70% to 99% stenosis without near-occlusion (RR 0.53, 95% CI 0.42 to 0.67). However, surgery decreased the five-year risk of any stroke or operative death in participants with near-occlusions (RR 0.95, 95% CI 0.59 to 1.53).

Rerkasem K, Orrapin S, Howard D et al. Carotid endarterectomy for symptomatic carotid stenosis. Cochrane Database Syst Rev. 2020. Art. No.: CD001081
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD001081.pub4/full

Evidence Level: I

Discharge Policy

Rehabilitation services improve the outcome for stroke patients?
A meta-analysis of 11 studies of multidisciplinary rehabilitation versus medical care (Evans, 1995) involving 2,183 patients found a significant difference in the odds of survival at discharge in favour of the rehabilitation group compared to controls (OR 1.46; 99% CI 1.13-1.78). More patients from rehabilitation programmes returned to their own homes at discharge (OR 2.08%; 99% CI 1.81-2.35) and were still there at follow-up (OR 1.87; 99% CI 1.57-2.17).
A Cochrane review (Stroke Unit Trialists' Collaboration, 2013) identified 21 trials (12,528 patients) which compared stroke unit care with general ward care and found that the former was associated with a reduction in deaths at one year follow up (OR 0.78, 95% CI 0.68 to 0.89)
A small systematic review of 3 trials of cardiovascular exercise post stroke (Meek, 2003) found insufficient evidence to establish benefit in terms of disability, impairment, extended activities of daily living, quality of life, or mortality.

Evans RL, Connis RT, Hendricks RD, et al. Multidisciplinary rehabilitation versus medical care: a meta-analysis. Soc Sci Med 1995;40:1699-706

Meek C, Pollock A, Potter J, et al. A systematic review of exercise trials post stroke. Clin Rehabil 2003;17:6-13
http://www.laterlifetraining.co.uk/wp-content/uploads/2011/01/Meek-et-al.-Clin-Rehab-2003.pdf

Stroke Unit Trialists' Collaboration. Organised inpatient (stroke unit) care for stroke. Cochrane Database Syst Rev. 2013, Art. No.: CD000197
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000197.pub3/full

Evidence Level: I

In previously fit and independent patients with occlusions to the CCA, ICA, M1, M2, ACA, basilar artery, or PCA consider mechanical thrombectomy if within 4.5 hours of symptom onset. Do not delay thrombolysis, this can be arranged once treatment has been started.
A randomised controlled trial looked at whether intraarterial treatment (i.e. arterial catheterization with a microcatheter to the level of occlusion and delivery of a thrombolytic agent, mechanical thrombectomy, or both) plus usual care would be more effective than usual care alone in patients with a proximal arterial occlusion in the anterior cerebral circulation that could be treated intraarterially within 6 hours after symptom onset (Berhemer, 2015). There was an absolute difference of 13.5 percentage points (95% CI, 5.9 to 21.2) in the rate of functional independence in favour of the intervention (32.6% vs. 19.1%). There were no significant differences in mortality or the occurrence of symptomatic intracerebral hemorrhage.
A study randomly assigned patients with ischemic stroke who were receiving 0.9 mg of alteplase per kilogram of body weight less than 4.5 hours after the onset of ischemic stroke either to undergo endovascular thrombectomy or to continue receiving alteplase alone (Campbell. 2015). Endovascular

therapy, initiated at a median of 210 minutes after the onset of stroke, increased early neurologic improvement at 3 days (80% vs. 37%, P=0.002) and improved the functional outcome at 90 days, with more patients achieving functional independence (71% vs. 40%; P=0.01). There were no significant differences in rates of death or symptomatic intracerebral hemorrhage.
A randomised controlled trial by Goya et al. (2015) evaluated rapid endovascular treatment in addition to standard care in patients with acute ischemic stroke. Rapid endovascular treatment was found to be better than standard care in terms of increasing functional independence (53.0%, vs. 29.3% in the control group; P<0.001) and reducing mortality (10.4%, vs. 19.0% in the control group; P=0.04).

Berkhemer OA, Fransen PS, Beumer D et al. A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke.N Engl J Med. 2015. 373:11-20
http://www.nejm.org/doi/full/10.1056/NEJMoa1411587#t=articleTop

Campbell BC, Mitchell PJ, Kleinig TJ et al. Endovascular Therapy for Ischemic Stroke with Perfusion-Imaging Selection. N Engl J Med. 2015. 372:1009-18

Goyal M, Demchuk AM, Menon BK et al. Investigators.Randomized Assessment of Rapid Endovascular Treatment of Ischemic. Stroke. N Engl J Med. 2015. 372:1019-30

Evidence Level: II

Prescribe metoclopramide 10 mg 8-hrly (5 mg if <50 kg body weight) to reduce the risk of pneumonia
A small (n=60) randomised controlled trial by Warusevitane (2015) found that metoclopramide may reduce the rate of pneumonia (rate ratio, 5.24; P<0.001) and may improve other clinical outcomes (aspiration, oxygen saturation, highest inflammatory markers, and National Institutes for Health Stroke Scale) in patients with subacute stroke fed via nasogastric tube.
A post hoc analysis of the randomized PRECIOUS trial (Prevention of Complications to Improve Outcome in Elderly Patients With Acute Stroke) concluded that in patients with stroke who had a nasogastric tube shortly after stroke onset, metoclopramide for 4 days did not reduce pneumonia or have an effect on the functional outcome (Sluis, 2024). A total of 1493 patients were enrolled with 1376 included in this analysis, of whom 1185 (86%) had ischemic stroke and 191 (14%) had intracerebral hemorrhage. The first day after randomization, 329 (23.9%) patients had a nasogastric tube, of whom 156 were allocated to metoclopramide and 173 to standard care. Metoclopramide was not associated with a reduction of pneumonia (41.0% versus 35.8%; adjusted OR 1.35 [95% CI, 0.79 to 2.30]).

Sluis WM, de Jonge JC, Reinink H et al. Metoclopramide to Prevent Pneumonia in Patients With Stroke and a Nasogastric Tube: Data From the PRECIOUS Trial. Stroke 2024;55:2402-8
https://pmc.ncbi.nlm.nih.gov/articles/PMC11419274/

Warusevitane A, Karuntilake D, Lally F, Sim J, Roffe C. The safety and effect of metoclopramide to prevent pneumonia in stroke patients fed via nasogastric tubes (MAPS Trial). Stroke 2015;46:454-60
http://stroke.ahajournals.org/content/early/2014/12/16/STROKEAHA.114.006639.full.pdf+html

Evidence Level: II

Patients with atrial fibrillation and a Chads≥ score 1, and contraindications to warfarin and to the newer non-vitamin K antagonist anticoagulants should be referred to cardiology for consideration of atrial appendage closure.
A randomised controlled trail by Reddy et al (2014) found that Percutaneous left atrial appendage closure was as good as warfarin for preventing the combined outcome of stroke, systemic embolism, and cardiovascular death (rate ratio, 0.60; 95% credible interval, 0.41-1.05), and superior to for preventing cardiovascular (hazard ratio, 0.40; 95% CI, 0.21-0.75; P = .005) and all-cause mortality (HR, 0.66; 95% CI, 0.45-0.98; P = .04).

Reddy VY, Sievert H, Halperin J, Doshi SK, et al. Percutaneous left atrial appendage closure vs warfarin for atrial fibrillation: a randomized clinical trial. JAMA. 2014;312:1988-98
http://jama.jamanetwork.com/article.aspx?articleid=1935122

Evidence Level: II

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