Current approach to acute stroke management

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Introduction
Ischaemic and haemorrhagic strokes are devastating illnesses. Globally, stroke is the second most common cause of death after ischaemic heart disease and the third most common cause of disability.1 In Australia, stroke deaths rank third behind heart disease and dementia. Ischaemic stroke represents approximately 80% of stroke in Australia and is generally less severe than primary intracerebral haemorrhage (ICH). The management of stroke could be divided into actions aimed at protecting individuals from stroke and actions aimed at treating individuals who have had a stroke. There have been major advances in both categories in Australia.

Stroke prevention
Much of the burden of stroke is preventable and there has been a marked improvement in the death rate from stroke in Australia over the past 40 years.2 From 1980 to 2016, the annual death rate from stroke, for individuals aged over 75, has fallen by almost two-thirds. Although the absolute death rate is much smaller for individuals aged between 55 and 75, the percentage reduction in mortality in this age group has been similar (Fig. 1).3

The biggest risk factor for stroke is age and the remarkable decrease in age-specific stroke rates has meant that the prevalence of stroke in Australia remained nearly constant, at 1.7%, from 2003 to 2015 despite the substantial increase in the elderly in Australia’s demographic profile.3 This reduction is likely to be the result of several public health measures although ascribing precise benefits to individual factors is difficult.

Australia was an early adopter of community-based treatment of vascular risk factors. The Busselton studies,4 surveyed an Australian community every 3 years from 1966 to 1981 and drove several interventions in treating hypertension, hyperlipidaemia, diabetes and smoking, as data from the Framingham Heart Study5 drove awareness of vascular risk factors. Cardiovascular medicines, the majority for treating vascular risk factors of hypertension and hyperlipidaemia, are subsidised by the Australian Government and are widely prescribed. In 2015, over 100 million Pharmaceutical Benefits Scheme (PBS)-subsidised prescriptions for cardiovascular medicines were dispensed.6

Hypertension is strongly associated with the risk of having any form of stroke and very strongly associated

Abstract
There have been marked improvements in the management of stroke in Australia over the past two decades. The greatest benefit has accrued from public health measures including reduced smoking rates and treatment of hypertension and hypercholesterolaemia. Recent advances in recanalisation therapy offer the chance of recovery to a subset of people who have a stroke. For many patients, stroke remains an illness with a devastating impact on their quality of life. Reducing the burden of stroke requires intervention across the health system from primary prevention through diagnosis, acute treatment, rehabilitation and secondary prevention. In this review, we will cover the changes in the epidemiology of stroke, public health measures in primary prevention of stroke, and acute management and secondary prevention of ischaemic stroke and primary intracerebral haemorrhage.
with risk of ICH. There has been a disproportionate fall in the incidence of ICH, relative to ischaemic stroke, in first-world countries including Australia, presumably due to treatment of hypertension in the community. This has reduced the overall burden of death and disability from ICH but the mortality and disability following an episode of ICH has remained constant reflecting the paucity of effective treatments.

Smoking as a vascular risk factor was first identified in the Framingham study. There has been a marked reduction in smoking in Australia over the past half century. In 1975, 41% of men and 29% of women were smokers. By 1990, the overall smoking rate was 28.4% and in 2018 the rate had fallen to 13.8%, one of the lowest in the first world. Smoking has a strong association with arterial plaque formation in general and with carotid plaque, which is a strong risk factor for ischaemic stroke. As smoking rates fall, the incidence of atheromatous carotid artery occlusion declines. In the United States, the rate of carotid endarterectomy, a proxy for severe carotid atheroma, fell from 298 per 100 000 in the year 2000 to 128 per 100 000 in 2014 without any increase in carotid stenting procedures.

As the incidence of stroke due to carotid disease, hypertension and ICH has fallen, the proportion of strokes in Australia attributable to an embolic source has increased. About one third of strokes have no obvious local small vessel or atheromatous cause and are likely to be due to emboli. The commonest source for these is thrombus formation in the left atrium, most commonly associated with atrial fibrillation. The incidence of atrial fibrillation increases markedly with age from 0.1% in those under 55 years to 10% in those over 80 years, so we can expect that our ageing population is going to be associated with an increasing incidence of embolic stroke. The increased recognition of the importance of atrial fibrillation and its treatment with direct-acting oral anticoagulants serves to counteract this demographic factor.

Diabetes is a demonstrated risk factor for ischaemic stroke with an age-specific incidence of stroke 2.9 times that of non-diabetic patients. Despite this, there is no good evidence that aggressive control of hyperglycaemia reduces the risk of stroke. The recent pandemic of diabetes and obesity has produced a population of patients with several metabolic factors that include obesity, glucose intolerance, hyperlipidaemia and hypertension. Currently, there is better evidence for targeting hypertension and hyperlipidaemia than the other components of this syndrome.

The prescription of antiplatelet agents for patients perceived as being at high risk of stroke is widespread. No trial has ever demonstrated a positive outcome for antiplatelet agents in primary prevention of stroke. There is a small benefit from the use of antiplatelet agents in prevention of a second event in patients who have had a stroke and this is discussed later.

Management of acute stroke: the evidence for treatment benefit

The acute management of patients who have had a stroke was, until recently, largely expectant and consisted mostly of supportive care and subsequent rehabilitation. Over the past 25 years, several interventions have been proven to reduce mortality and morbidity in stroke. Some interventions, such as endovascular thrombectomy (EVT), offer selected patients the potential for complete recovery from what would, otherwise, have been a catastrophic life event. Despite this, only a small minority of patients presenting with stroke are eligible for thrombolysis and recanalisation therapies and stroke prevention remains the primary aim of stroke care.

Stroke units

Patients experiencing an acute stroke benefit from admission to a stroke unit, a geographically defined unit with co-located beds. Stroke units are staffed by a multidisciplinary team that includes medical, nursing and allied health staff with expertise in stroke and rehabilitation. Stroke units typically provide monitoring of blood pressure (BP) and pulse parameters and frequent monitoring of clinical signs, typically using the National Institutes of Health Stroke Scale. Cardiac monitoring for at least 24 h is also recommended but not always available. Stroke units aim to prevent complications such as
aspiration pneumonia and deep venous thrombosis, establish secondary prevention measures and facilitate early rehabilitation. They have formalised management protocols that seek to reflect the best current practice.

Organised stroke unit care significantly reduces death, disability and institutionalisation when compared to conventional care. The magnitude of the effect equates to two extra survivors, six more patients living at home and six more living independently for every 100 patients receiving stroke unit care. This effect is independent of age, gender and stroke severity or type. Why stroke units offer such a marked and reproducible benefit is uncertain. In one of the few positive studies, a multidisciplinary nurse-supported care bundle to manage fever, hyperglycaemia and swallowing was shown to improve survival. Structured rehabilitation after stroke is conducted in stroke units, but it has been difficult to demonstrate a clear benefit from this. A large trial of very early mobilisation within the first 24 h showed evidence of harm compared to standard treatment. It seems likely that a dedicated unit ensures the uniform delivery of best practice care and that the total of many small interventions may sum to a benefit where trials of individual interventions do not reach significance.

**Antiplatelet agents and anticoagulation (administration and timing)**

**Acute ischaemic stroke**

Antiplatelet agents have been shown to reduce significantly, albeit slightly, the risk of recurrent stroke in patients who have had an ischaemic stroke and who do not have atrial fibrillation. Patients who are not eligible for thrombolysis should be started on antiplatelet therapy as soon as an ICH is excluded by brain imaging. In patients who undergo reperfusion therapy, the introduction of antiplatelet agents is generally delayed by 24 h and commenced after exclusion of a haemorrhage on brain imaging at 24 h.

**Minor stroke and transient ischaemic attack**

Dual antiplatelet agent therapy should be started within 24 h in patients with minor strokes (NIHSS score < 3–4) and in those with high-risk transient ischaemic attack (TIA) where these are defined by patients having ABCD2 scores greater than or equal to 4 (ABCD2 scoring: age > 60 (1), BP > 140 systolic (1) or > 90 diastolic (1), clinical picture that includes weakness (2) or aphasia (1), presence of diabetes (1) and duration, 10–59 min (1) greater than 60 min (2)). This intervention has been shown to lead to 19 fewer recurrent strokes per 1000 patients in the first 90 days. The benefit of dual antiplatelet therapy occurs early but with time the risk of haemorrhage accumulates; because of this balance between risk and benefits, the period of dual antiplatelet therapy should be limited to 3 weeks.

The Australian guidelines recommend a loading dose of aspirin and clopidogrel followed by 100–150 mg aspirin and 75 mg clopidogrel daily for a total of 21 days, and a single antiplatelet agent thereafter. The use of a proton-pump inhibitor should be considered during the dual antiplatelet period for patients with symptomatic reflux or a history of gastrointestinal bleeding.

**Stroke or TIA related to atrial fibrillation**

The identification of atrial fibrillation is one of the key benefits of admission to a stroke unit. Where there is a strong suspicion of an embolic source, then the search for atrial fibrillation should extend beyond the period of in-patient monitoring. Anticoagulation should be started in every ischaemic stroke patient found to be in permanent or transient atrial fibrillation unless there is a definite contraindication. Historical observational data, including data from the control groups of randomised trials, show that, without anticoagulation, the risk of early recurrent stroke in the first 14 days after atrial fibrillation-related ischaemic stroke is between 0.5% and 1.3% per day. Although patients with large vessel strokes who have no distal atheroma are presumed to have an embolic source, there is no evidence that systemic anticoagulation is helpful in the absence of atrial fibrillation.

The re-introduction of anticoagulation after stroke is a balance between the risk of recurrent stroke and the risk of haemorrhage into dead cerebral tissue. There is little evidence to help with the timing of this. As a rule of thumb, the 1–3–6–12 day rule is advocated: anticoagulation is re-instituted after 1 day in patients with TIA, after 3 days in the presence of a small, non-disabling infarct and after 6 days in patients with a moderate stroke. Patients with large infarcts involving most of a major cerebral arterial territory do not have anticoagulation re-instituted until 2 or even 3 weeks has elapsed.

**BP lowering in acute stroke**

**Intracerebral haemorrhage**

The mortality and morbidity associated with ICH have remained very resistant to intervention. One of the few positive interventions with an evidence base has been acute lowering of BP. The INTERACT2 trial suggests that lowering BP in the acute phase of ICH improves functional outcome. Australian guidelines adopted
after this trial recommend a target of ~140 mmHg systolic BP in the acute post-stroke period. Despite BP lowering being found safe in clinical trials of mild to moderate ICH, the effect on mortality and dependency remains controversial.\textsuperscript{35}

**Acute ischaemic stroke**

In ischaemic stroke, current guidelines suggest that BP should not be lowered acutely unless patients have a BP of 220/100 or more or are eligible for treatment with intravenous thrombolysis (IVT) in which case the target is below 185/110 mmHg before treatment and in the first 24 h after treatment. Most stroke units seek gradually to normalise BP during hospitalisation after an acute ischaemic stroke and will start or restart antihypertensive therapy in patients with a BP higher than 140/90 mmHg unless there is a contraindication.\textsuperscript{18}

**Reperfusion therapies**

Ideal treatment of stroke is re-establishment of blood flow to regions of ischaemic brain before irreversible tissue necrosis occurs. This requires careful patient selection, effective reperfusion and rapid implementation.

**Intravenous thrombolysis**

IVT is the chemical lysis of blood clots within blood vessels, using an intravenous infusion of fibrinolytic medication. IVT can be undertaken in a setting where appropriate infrastructure and support are available. The minimum requirements include CT imaging and support from a stroke physician, either locally or via telemedicine. It is widely available in Australian cities and regional centres and is effective in improving patient outcomes.\textsuperscript{36} The most commonly used agent is recombinant tissue plasminogen activator or alteplase at a dose of 0.9 mg/kg, given as a 10% bolus followed by a 1-h infusion of the remaining dose with a 90 mg total dose maximum.\textsuperscript{37,38} The major risk associated with the use of alteplase is cerebral haemorrhage. As the time from stroke onset increases, the risk of bleeding remains constant but the chance of benefit is reduced and the risk to benefit crossover occurs at about 4.5 h.\textsuperscript{39,40} A smaller dose of 0.6 mg/kg is used in some jurisdictions including Japan.\textsuperscript{41} The use of alteplase provides an overall benefit of approximately a 30% relative increased chance of having little or no residual disability.\textsuperscript{42} This occurs at a risk of bleeding, most seriously of symptomatic ICH. Symptomatic ICH occurs in 2% to 10% of trial patients and asymptomatic bleeding in 20% to 30% of patients.\textsuperscript{39} ICH often occurs in the infarcted brain tissue as ‘haemorrhagic transformation’ but may occur elsewhere in the brain. The size and the severity of an ICH may vary from a small petechial bleed with little clinical implication to lobar haemorrhage with mass effect and life-threatening neurological deterioration.

Alteplase is effective when given early, but its efficacy decreases sharply with time. The number needed to treat (NNT) for one patient to return to independence rather than a lifetime of disability is 4.5 within 1.5 h of onset, and this NNT increases steadily with time so that at 4.5 h, 14 patients have to be treated for the same benefit.\textsuperscript{36} The 4.5 h cut-off is based on trials using relatively unsophisticated imaging, and it is likely that there is a sub-population who have little or no brain infarction at this time who stand to benefit from later thrombolysis. Recently, the EXTEND trial\textsuperscript{43} showed a benefit of alteplase in both large-vessel occlusions (LVO) and small-vessel occlusions in patients selected using advanced imaging in the 4.5–9 h time window, providing supportive evidence for widening the treatment time window in selected patients.

IVT has a limited ability to reopen occluded vessels with subsequent reperfusion of the area supplied by the blocked artery. This is especially the case in occlusions of large vessels. Depending on the vessel diameter and the clot burden, IVT will open approximately 30% of vessels. There is also a group of patients where the artery re-ocludes despite initial success. These patients comprise 14–34% of the group with initially recanalised arteries.\textsuperscript{44–46} Because of these limitations with alteplase, other agents, such as tenecteplase, have been explored and considerable research has been conducted in endovascular clot retrieval or thrombectomy.

Tenecteplase is used as an alternative to alteplase in some Australian hospitals.\textsuperscript{47} Tenecteplase has been shown to increase recanalisation rates from 10% to 22% when given at a dose of 0.25 mg/kg in patients selected for LVO.\textsuperscript{48} Tenecteplase has also been shown to have a trend towards higher efficacy than alteplase in a recent metaanalysis.\textsuperscript{49–50} As a result, tenecteplase as an alternative to alteplase has been added to the Australian Stroke Guidelines although trials are ongoing to confirm superiority and non-inferiority of tenecteplase when compared to alteplase in reducing rates of death and dependency.\textsuperscript{51}

**Endovascular thrombectomy**

Since 2015, multiple randomised trials have shown a benefit of EVT over standard care, generally IVT, for patients with anterior circulation strokes because of LVO up to 6 (3 trials), 8 (1 trial) and 12 h (1 trial) after stroke onset.\textsuperscript{52} The trials showed that the benefit of direct intervention extended to patients who had not received intravenous alteplase, and to patients who presented more than 300 min from stroke symptom onset. Based on this metaanalysis, the Australian guidelines...
recommend starting thrombectomy within 6 h of onset. More recently, the DAWN\textsuperscript{53} and DEFUSE3\textsuperscript{54} trials have shown that, with advanced imaging, a proportion of patients, with occluded large vessels but excellent collateral circulation, can be identified who will benefit from reperfusion up to 24 and 16 h, respectively, following stroke onset. The number of patients with resuable tissue declines relentlessly with time and the fact that a small percentage of patients may receive a benefit late in no way reduces the need for urgency in assessment and intervention in patients with stroke.

Over the last 4 years, the increasingly sophisticated application of thrombolysis and interventional clot retrieval, alone or in combination, using advanced imaging-based selection, has led to a major growth in the implementation of reperfusion therapies. Broadening the availability of these therapies requires substantial reorganisation of health services. Strategies aimed at improving service delivery include improving regional imaging, providing tele-health support in regional and remote areas, and organising transport services to reduce the time needed to get patients to high-level stroke services that offer interventional therapies.

**Carotid endarterectomy and stenting**

The presence of carotid atheroma is a strong risk factor for stroke. The incidence of carotid stenosis is declining with time, presumably due to reduced smoking rates and the implementation of medical therapy for vascular risk factors. Patients who have a symptomatic carotid stenosis, defined by the occurrence of an ipsilateral stroke or TIA, benefit from surgical treatment. The most benefit is seen in patients with a severe (70–99\%) stenosis with a smaller benefit in patients with moderate (50–69\%) stenosis.\textsuperscript{55}

The risk of recurrent stroke declines rapidly after the initial event and surgery should be done early with most stroke risk occurring in the first 2 weeks.

The large carotid artery surgical intervention studies recruited before the availability of current best medical treatment; there is ongoing research comparing best medical management with surgery or stenting in addition to best medical management.\textsuperscript{56} This may reset the guidelines for carotid surgery. The benefits of surgery on asymptomatic carotid stenosis are marginal.

In general, carotid endarterectomy is the preferred procedure. Carotid stenting achieves the same goals but with a higher peri-procedural stroke risk. Stenting may be justified where the operative risk is high or the carotid anatomy makes surgical endarterectomy implausible.

**Prevention of recurrent stroke after an initial event**

The acute treatment of stroke overlaps into secondary prevention as discussed earlier. Once the first 90 days have elapsed after a stroke, the treatments that are supported by evidence are as follows: smoking cessation, use of a single antiplatelet drug, lowering of serum lipids, lowering of BP and treatment of non-valvular atrial fibrillation with an antiplatelet. In addition, guidelines\textsuperscript{57} have suggested lifestyle and behavioural changes including limiting alcohol consumption, weight control, daily moderate-to-high physical activity, salt restriction and a Mediterranean diet. There is some evidence of an effect of the combination of these changes in prospective studies.\textsuperscript{58}

There is evidence to suggest that there is no lower limit to either BP or serum lipids in lowering stroke risk, but this has to be balanced against the increasing likelihood of symptomatic side effects with a consequent loss of compliance. A systolic BP target of less than 140 mmHg and a diastolic target of less than 90 mmHg are reasonable in clinical practice with tightening to a target of less than 120/80 for high-risk patients. A target of low-density lipoprotein cholesterol of 1.8 mmol/L is recommended.\textsuperscript{59,60}

**Post-acute hospital rehabilitation and life after stroke**

The management of stroke patients after their discharge from hospital involves their family and friends, multidisciplinary teams, in-patient rehabilitation services, and stroke and community organisations. There is evidence that person-centred, self-directed rehabilitation intervention improves quality of life.\textsuperscript{61} Detailed guidance on rehabilitation, return to family life, work and driving are an important part of stroke recovery, which goes beyond the scope of this review.

**Conclusion**

Australia has had significant success in reducing the age-specific incidence of stroke, in improving the outlook of people presenting with ischaemic stroke and in reducing the risk of recurrent stroke in stroke survivors. Smoking cessation, treatment of hypertension, treatment of hyperlipidaemia and identification of atrial fibrillation are the most effective stroke therapies. Improvements in the organisation of stroke service delivery offers the hope of effective therapy for acute stroke being available to more stroke victims with little increase in overall health spending.
References

1 Global Burden of Disease Lifetime Risk of Stroke Collaborators, Feigin VL, Nguyen G, Cercy K, Johnson CO, Alam T et al. Global, regional, and country-specific lifetime risks of stroke, 1990 and 2016. *N Engl J Med* 2018; 379: 2429–37.

2 O’Donnell M, Xavier D, Diener C, Sacco R, Lisheng L, Zhang H et al. Rationale and design of INTERSTROKE: a global case-control study of risk factors for stroke. *Neuroepidemiology* 2010; 35: 36–44.

3 Australian Institute of Health and Welfare. *Australia’s Health 2018* ASHSN, AUS 221. Canberra: AIHW; 2018 Chapter 3, Page 2.

4 Knuiman MW, Cullen KJ, Bulsara MK, Welborn TA, Hobbs MS. Mortality trends, 1965 to 1989, in Busselton, the site of repeated health surveys and interventions. *Aust J Public Health* 1994; 18: 129–35.

5 Mahmood SS, Levy D, Vasan RS, Wang TJ. The Framingham heart study and the epidemiology of cardiovascular disease: a historical perspective. *Lancet* 2014; 383: 999–1008.

6 Australian Institute of Health and Welfare. *Medicines for cardiovascular disease, Cat. no. CVD. Canberra: AIHW;* 2017: 80.

7 Zahuranec DB, Lisabeth LD, Sanchez BN, Smith MA, Brown DL, Garcia NM et al. Intracerebral hemorrhage mortality is not changing despite declining incidence. *Neurology* 2014; 82: 2180–6.

8 Gray NJ, Hill DJ. Patterns of tobacco smoking in Australia. *Med J Aust* 1975; 2: 819–22.

9 Greenhalgh E, Scollo MM, Winstanley MH. *Tobacco in Australia: Facts and issues*. Melbourne: Cancer Council Victoria; 2020. Available from URL: www.TobaccoInAustralia.org.au.

10 Lichtman JH, Jones MR, Leifheit EC, Sheffet AJ, Howard G, Lal BK et al. Carotid endarterectomy and carotid artery stenting in the US medicare population, 1999-2014. *JAMA* 2017; 318: 1035–46.

11 Diener HC, Sacco RL, Easton JD, Granger CB, Bernstein RA, Uchiyama S et al. Dabigatran for prevention of stroke after embolic stroke of undetermined source. *N Engl J Med* 2019; 380: 1906–17.

12 Fonseca AC, Ferro JM. Cryptogenic stroke. *Eur J Neurol* 2015; 22: 618–23.

13 Ntaios G, Pearce LA, Velkamp R, Sharma M, Kasner SE, Korompoki E et al. NAVIGATE ESUS investigators. Potential embolic sources and outcomes in embolic stroke of undetermined source in the NAVIGATE-ESUS trial. *Stroke* 2020; 51: 1797–804.

14 Kannel W, Healey JS. Cardioembolic stroke. *Circ Res* 2017; 120: 514–26.

15 Air EL, Kissela BM, Diabates, the metabolic syndrome, and ischemic stroke: epidemiology and possible mechanisms. *Diabetes Care* 2007; 30: 3131–40.

16 Stroke Unit Trialists’ Collaboration. Collaborative systematic review of the randomised trials of organised patient (stroke unit) care after stroke. *BMJ* 1997; 314: 1151–9.

17 Brott T, Adams HP Jr, Olinger CP, Marler JR, Barsan WG, Biller J et al. Measurements of acute cerebral infarction: a clinical examination scale. *Stroke* 1989; 20: 864–70.

18 Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2019; 50: e344–418.

19 Stroke Unit Trialists’ Collaboration. Organised inpatient (stroke unit) care for stroke. *Cochrane Database Syst Rev* 2013: 9: CD00197.

20 Langhorne P, Ramachandra S, Stroke Unit Trialists’ Collaboration. Organised inpatient (stroke unit) care for stroke: network meta-analysis. *Cochrane Database Syst Rev* 2020: 4: CD00198.

21 Indredavik B, Bakke F, Sildahl SA, Rokseth R, Haheim LL. Treatment in a combined acute and rehabilitation stroke unit: which aspects are most important? *Stroke* 1999; 30: 917–23.

22 Middleton S, McEllduff P, Ward J, Grimshaw JM, Dale S, d’Este C et al. Implementation of evidence-based treatment protocols to manage fever, hyperglycaemia, and swallowing dysfunction in acute stroke (QASC): a cluster randomised controlled trial. *Lancet* 2011; 378: 1699–706.

23 Middleton S, Coulahan K, Mmazagneran G, Low Choy N, Dale S, Jammali-Blasi A et al. Mortality reduction for fever, hyperglycaemia, and swallowing nurse-initiated stroke intervention: QASC trial (quality in acute stroke care) follow-up. *Stroke* 2017; 48: 1331–6.

24 Berndhardt J, English C, Johnson L, Cumming TB. Early mobilization after stroke: early adoption but limited evidence. *Stroke* 2015; 46: 1141–6.

25 The AVERT Trial Collaboration Group. Efficacy and safety of very early mobilisation within 24 h of stroke onset (AVERT): a randomised controlled trial. *Lancet* 2015; 386: 46–55.

26 Committee Capri Study. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE steering committee. *Lancet* 1996; 348: 1329–39.

27 Jadhav AP, Molyneaux BJ, Hill MD, Jovin TG. Care of the post-thrombectomy patient. *Stroke* 2018; 49: 2801–7.

28 Wang Y, Wang Y, Zhao X, Liu L, Wang D, Wang C et al. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. *N Engl J Med* 2013; 369: 11–19.

29 Johnston SC, Easton JD, Farrant M, Barsan W, Conwit RA, Elm J et al. Clopidogrel and aspirin in acute ischemic stroke and high-risk TIA. *N Engl J Med* 2018; 379: 215–25.

30 Hart RG, Coull BM, Hart D. Early recurrent embolism associated with nonvalvular atrial fibrillation: a retrospective study. *Stroke* 1983; 14: 688–93.

31 Hart RG, Sharma M, Mundil H, Kasner SE, Bangdiwala SI, Berkowitz SD et al. Rivaroxaban for stroke prevention after embolic stroke of undetermined source. *N Engl J Med* 2018; 378: 2191–201.

32 Heidbuchel H, Verhamme P, Alings M, Antz M, Hacke W, Oldgren J et al. European heart rhythm association practical guide on the use of new oral anticoagulants in patients with nonvalvular atrial fibrillation: executive summary. *Eur Heart J* 2013; 34: 2094–106.

33 Anderson CS, Heeley E, Huang Y, Wang J, Stapf C, Delcourt C et al. Rapid blood-pressure lowering in patients...
with acute intracerebral hemorrhage. N Engl J Med 2013; 368: 2355–65.
34 Stroke Foundation. Clinical Guidelines for Stroke Management. Melbourne, Australia: Stroke Foundation; 2020.
35 Boulouis G, Morotti A, Goldstein JN, Charidimou A. Intensive blood pressure lowering in patients with acute intracerebral haemorrhage: clinical outcomes and haemorrhage expansion. Systematic review and meta-analysis of randomised trials. J Neurol Neurosurg Psychiatry 2017; 88: 339–45.
36 Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. Lancet 2014; 384: 1929–35.
37 Brott TG, Haley EC Jr, Levy DE, Barsan W, Broderick J, Shepperd GL et al. Urgent therapy for stroke. Part I. Pilot study of tissue plasminogen activator administered within 90 minutes. Stroke 1992; 23: 632–40.
38 Haley EC Jr, Levy DE, Brott TG, Shepperd GL, Wong MC, Kongable GL et al. Urgent therapy for stroke. Part II. Pilot study of tissue plasminogen activator administered within 91–180 minutes from onset. Stroke 1992; 23: 641–5.
39 Hacke W, Donnan G, Fieschi C, Kaste M, von Kummer R, Broderick JP et al. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. Lancet 2004; 363: 768–74.
40 Hacke W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med 2008; 359: 1317–29.
41 Yamaguchi T, Mori E, Minematsu K, Nakagawara J, Hashi K, Saito I et al. Alteplase at 0.6 mg/kg for acute ischemic stroke within 3 hours of onset: Japan alteplase clinical trial (J-ACT). Stroke 2006; 37: 1810–15.
42 National Institute of Neurological Diseases, Stroke rt-PA Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995; 333: 1581–7.
43 Campbell BC, Mitchell PJ, Churilov L, Yassi N, Kleining TJ, Yan B et al. Tenecteplase versus alteplase before endovascular thrombectomy (EXTEND-IA TNK): a multicenter, randomized, controlled study. Int J Stroke 2018; 13: 328–34.
44 Janjua N, Alkawi A, Suri MFK, Qureshi AI. Impact of arterial recanalization and distal fragmentation during thrombolysis among patients with acute ischemic stroke. Am J Neuroradiol 2008; 29: 253–8.
45 Rha LJ-H, Saver LJ. The impact of recanalization on ischemic stroke outcome: a meta-analysis. Stroke 2007; 38: 967–73.
46 Rubiera FM, Alvarez-Sabin AJ, Ribo AM, Montaner AJ, Santamartina AE, Arenillas AJ et al. Predictors of early arterial recanalization after tissue plasminogen activator-induced recanalization in acute ischemic stroke. Stroke 2005; 36: 1452–6.
47 Parsons M, Churilov L, Schutte AE, Levi C. Tenecteplase (and common sense) in short supply during the COVID-19 pandemic. Med J Aust 2020; 213: 442–443.e1.
48 Campbell BVC, Mitchell PJ, Churilov L, Yassi N, Kleining TJ, Dowling RJ et al. Tenecteplase versus alteplase before thrombectomy for ischemic stroke (report). N Engl J Med 2018; 378: 1573–82.
49 Saver JL, Goyal M, van Der Lugt A, Menon BK, Majoei CBLM, Dippel DW et al. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: a meta-analysis. JAMA 2016; 316: 1279–89.
50 Huang X, Macisaa R, Thompson JL, Levin B, Buchsbaum R, Haley EC et al. Tenecteplase versus alteplase in stroke thrombectomy: an individual patient data meta-analysis of randomized controlled trials. Int J Stroke 2016; 11: 534–43.
51 Logallo N, Novotny V, Assmus J, Kvistad CE, Atelhöld L, Ronning OM et al. Tenecteplase versus alteplase for management of acute ischaemic stroke (NOR-TEST): a phase 3, randomised, open-label, blinded endpoint trial. Lancet Neurol 2017; 16: 781–8.
52 Goyal M, Menon BK, van Zwam WH, Dippel DWJ, Mitchell PJ, Demchuk AM et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet 2016; 387: 1723–31.
53 Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct (report). N Engl J Med 2018; 378: 11–21.
54 Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. N Engl J Med 2018; 378: 708–18.
55 Orrapin S, Rerkasem K. Carotid endarterectomy for symptomatic carotid stenosis. Cochrane Database Syst Rev 2017; 6: CD001081.
56 Mott M, Koroshetz W, Wright CB. CREST-2: identifying the best method of stroke prevention for carotid artery stenosis: National Institute of Neurological Disorders and stroke organizational update. Stroke 2017; 48: e130–1.
57 Kornan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ekekowitz MD et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2014; 45: 2160–236.
58 Zhang Y, Tuomilehto J, Jousilahti P, Wang Y, Antikainen R, Hu G. Lifestyle factors on the risks of ischemic and hemorrhagic stroke. Arch Intern Med 2011; 171: 1811–18.
59 Diener HC, Hankey GJ. Primary and secondary prevention of ischemic stroke and cerebral hemorrhage: JACC focus seminar. J Am Coll Cardiol 2020; 75: 1804–18.
60 Amarenco P, Kim JS, Labreuche J, Charles H, Abtan J, Bejot Y et al. A comparison of two LDL cholesterol targets after ischemic stroke. N Engl J Med 2020; 382: 9–19.
61 Fu V, Weatherall M, McPherson K, Taylor W, McRae A, Thomson T et al. Taking charge after stroke: a randomized controlled trial of a person-centered, self-directed rehabilitation intervention. Int J Stroke 2020; 15: 954–64.