Acute Stroke Emergency Management

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Case Presentation

A 53-year-old woman with a history of atrial fibrillation, smoking, arterial hypertension, diabetes mellitus, and previous transient ischemic attack (TIA) with left lower extremity weakness; presented within 30 min of a sudden loss of right-sided motor function of both the upper and lower extremity, a profound global aphasia, a right facial droop and a gaze deviation to the left. Her presenting National Institutes of Health Stroke Scale (NIHSS) score was 18. At the time of presentation to the hospital her platelet count was 250 k, white blood cell count was 8.8 K, and coagulation factors (aPTT, PT/INR) were within normal limits. Her blood pressure was 170/90, heart rate was 110 and irregularly irregular and respiratory rate was 17. She was protecting her airway while in the emergency department. Her home medications were listed as lisinopril 20 mg and aspirin 81 mg, both of which her husband stated, "she hadn't filled in years." She was immediately taken for head computed tomography (CT) which was unrevealing except for a small hyperdensity at the location of the left middle cerebral artery origin (Fig. 35.1). She then underwent a CT angiography of the neck and brain vessels that revealed a cut off of the left middle cerebral artery (Fig. 35.2). She was immediately dosed with intravenous tissue plasminogen activator (IV tPA).

Question What approach should guide the remainder of this patient's acute stroke management?

Answer Emergent endovascular thrombectomy

All patients with acute ischemic stroke (AIS) who present within 6 h of symptoms onset should be evaluated for IV tPA and/or acute endovascular therapy. IV tPA ideally should be dosed within 3 h of symptoms onset, with better outcomes directly correlated to shorter door to thrombolytic times. This patient, following a head CT that revealed no hemorrhage and not having any other contraindication, was started on IV tPA. The stroke and neuroradiology teams reviewed her imaging and calculated an Alberta Stroke Program Early CT Score (ASPECTS) of greater than 7. She was taken expeditiously to the angiography suite where an NIHSS score by the stroke team was repeated, revealing little to no clinical improvement, and was

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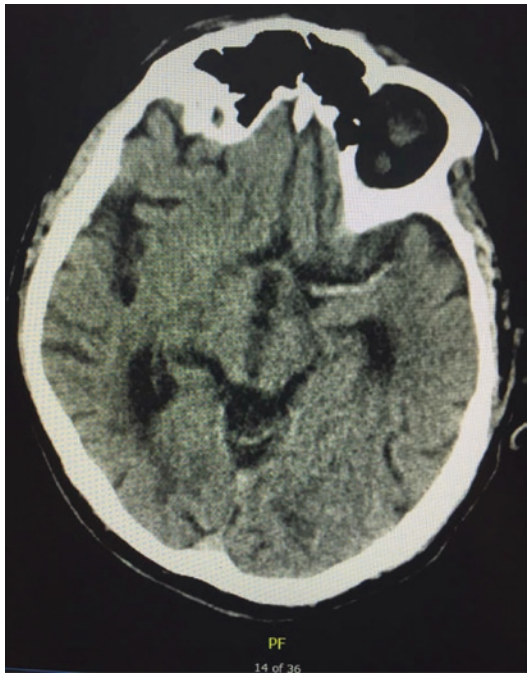

Fig. 35.1 Hyperdense LMCA sign

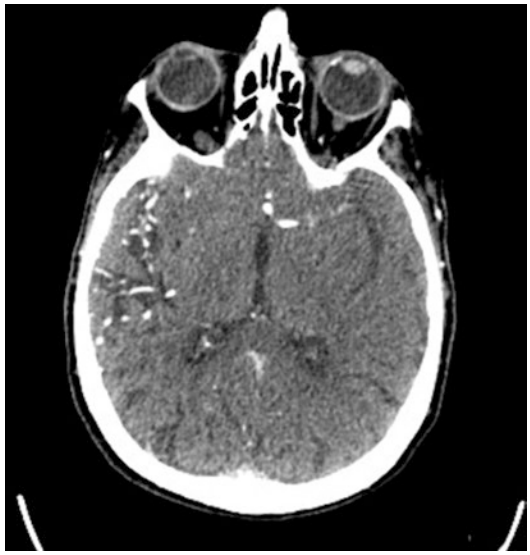

Fig. 35.2 Acute LMCA cut-off

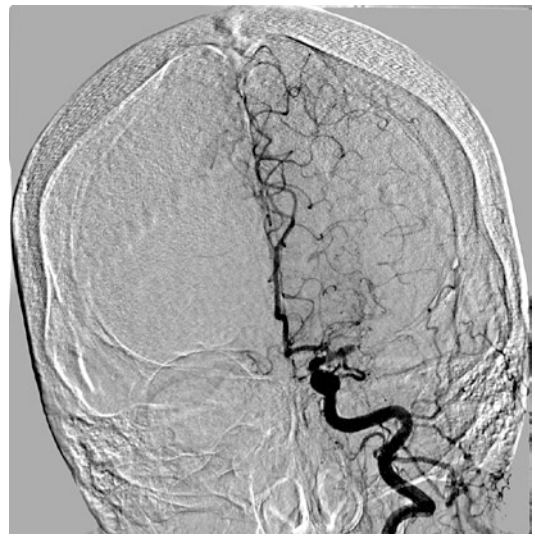

Fig. 35.3 Acute LEFT middle cerebral artery cut-off seen on digital subtraction angiogram

subsequently started on conscious sedation with midazolam and fentanyl in preparation for endovascular thrombectomy. Neuro-endovascular specialists performed an emergent cerebral diagnostic angiogram (Fig. 35.3), which revealed a persistent left middle cerebral artery occlusion. A stent-retriever device was deployed in the area of occlusion for roughly 2–3 min (Fig. 35.4). Following the single pass attempt, the stent-retriever was pulled with intact clot noted, which was integrated within the stent mesh upon device removal. A confirmatory angiogram was shot immediately following the thrombectomy procedure showing complete recanalization of the left middle cerebral artery with no distal artery cut-off (Fig. 35.5). The patient was then brought to the neurological critical care unit where vital signs and comprehensive neurological assessments were completed every hour for 24 h. Her systolic blood pressure was kept below 180 mmHg and glucose checks were instituted every 4 h with a goal to maintain euglycemia (glucose 80–200 mg/dL). Within a few hours, the patient was able to move her right upper and lower extremity against gravity, her forced gaze deviation was resolved and she was able to follow simple commands. One day later, the patient began speaking more fluently and was able to sit in a chair and tolerate a regular diet. An MRI was completed within 48 h of the endovascular procedure that showed a very small ischemic stroke core on diffusion-weighted imaging and T2 fluid attenuated (FLAIR) imaging. She also underwent an echocardiogram that revealed a 65% ejection fraction,

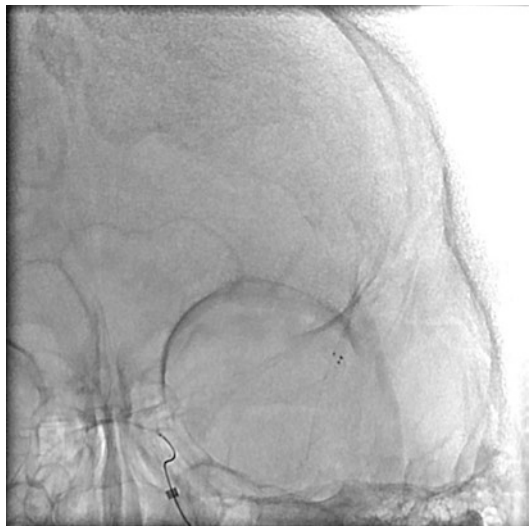

Fig. 35.4 Deployment of stent-retriever into the area of occlusion for roughly 2–3 min

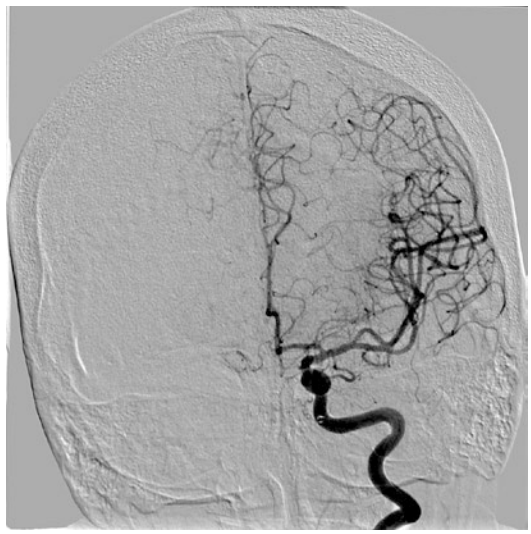

Fig. 35.5 Confirmatory angiogram showing recanalization of the LEFT middle cerebral artery

moderate left atrial enlargement and no apical thrombus. Her CHA_2DS_2 -VASc was calculated as a 5, and she was started on a regimen of enoxaparin (1 mg/kg) twice daily for secondary stroke prevention as a bridge to the novel anticoagulant apixaban during an outpatient follow-up stroke appointment. The patient continued to make improvements in neurological status and was transferred out of the ICU 2 days after the endovascular therapy with full strength on the right side of her body and only minimal word finding difficulties.

Principles of Management

Diagnosis

Acute ischemic stroke remains a clinical diagnosis that should be made within the first minutes of a patient entering the emergency department. Tools such as the NIHSS (Table 35.1) help to assess and communicate stroke symptom severity, however in the presence of an acute, focal neurological change, stroke should always be strongly considered. Ideally an initial head CT should be completed as soon as possible and within 25 min of patient arrival to assess for acute intracranial pathology, such as intracranial hemorrhage [1, 2]. If the CT scan is negative for pathology, the patient meets time criteria, does not have a contraindication, and continues to have a neurological deficit suggestive of acute ischemic stroke, IV tPA should be administered [1]. A CT angiogram of the head and neck to assess vessel status, perfusion status and possible vessel occlusion can be completed at the time of the initial CT scan so long as it does not delay the delivery time of IV tPA [1]. An MRI with diffusion-weighted imaging (MRI-DWI) in the stroke patient can be used to show areas of restricted diffusion of water that correspond to areas of acute ischemia. Unlike the head CT for acute stroke imaging, findings on MRI-DWI generally appear within minutes of ischemia.

Acute Stroke Management, tPA Administration

The goal for AIS therapy focuses on revascularization with IV tPA ideally within 45 min of arrival and no later than 1 h after arrival [1, 2]. Once a negative CT result is obtained, the threshold for starting tPA falls to the treating clinician, taking into account the severity of stroke symptoms by NIHSS, the bleed risk of the patient and any known contraindications such as recent

Table 35.1 NIHSS scoring

1A – Level of consciousness
Alert; keenly responsive (score 0)
Arouses to minor stimulation (score 1)
Requires repeated stimulation to arouse or painful stimulation (score 2)
Unresponsive, only reflexic posturing (score 3)
1B – Communication – Ask "What Month is it? How old are you?"
Both questions correct (score 0)
Only 1 question answered correctly or if the patients is intubated or has a language barrier (score 1)
No questions answered correctly/aphasic (score 2)
1C – Command following – Ask patient to "Blink eyes" and "Squeeze Hands"
Performs both tasks correctly (score 0)
Performs one task correctly (score 1)
Performs none correctly (score 2)
2 – Horizontal eye movements
No gaze deviation, palsy (Score 0)
Partial Gaze Palsy: Can be overcome (Score 1)
Forced Gaze Palsy: Cannot be overcome, even with oculocephalic reflex (Score 2)
3 – Visual fields
No Visual Loss (Score 0)
Partial Hemianopia (Score 1)
Complete Hemianopia (Score 2)
Blind or Bilateral Hemianopia (Score 3)
4 – Facial weakness
Normal symmetry (Score 0)
Minor paralysis, flattened nasolabial fold, smile asymmetry (Score 1)
Partial paralysis, Lower Face only (Score 2)
Complete paralysis, upper and lower face (Score 3)
5a – Left arm: Ask patient to hold LEFT arm up for 10 s
No drift 10 s, or amputee (score 0)
Drift, but doesn't hit the bed (score 1)
Drift, but it does hit the bed (score 2)
Is not able to effort against gravity (score 3)
No movement at all (score 4)
5B – Right arm: Ask patient to hold RIGHT arm up for 10 s
No drift 10 s, or amputee (score 0)
Drift, but doesn't hit the bed (score 1)
Drift, but it does hit the bed (score 2)
Is not able to effort against gravity (score 3)
No movement at all (score 4)
6A – Left leg: Ask patient to hold LEFT leg up for 5 s
No drift for 5 s, or amputee (score 0)
Drift, but doesn't hit the bed (score 1)
Drift, but it does hit the bed (score 2)
Is not able to lift against gravity (score 3)
No movement at all (Score 4)
6B – Right leg: Ask patient to hold LEFT leg up for 5 s
No drift for 5 s, or amputee (score 0)
Drift, but doesn't hit the bed (score 1)
Drift, but it does hit the bed (score 2)
Is not able to lift against gravity (score 3)
No movement at all (score 4)
7 – Ataxia: finger to nose and heel to shin testing
No ataxia noted, patient aphasic, patient paralyzed (score 0)
Ataxia noted in 1 limb (score 1)
Ataxia noted in 2 limbs (score 2)
8 – Sensation: testing pain, light touch, vibration sensation bilaterally
Normal sensation bilaterally (score 0)
Mild-moderate unilateral loss of sensation (score 1)
Complete unilateral loss of sensation or unresponsive (score 2)
9 – Language: testing naming of objects, reading simple sentences, describing a scene
Normal (score 0)
Mild – moderate aphasia, decreased ability to communicate but is able to get most ideas out (score 1)
Severe aphasia – very difficult to communicate, unable to have effective communication (score 2)
Mute/global aphasia or coma – no speech or auditory comprehension (score 3)
10 – Dysarthria: repeat or read words testing different parts of the tongue
Normal speech (score 0)
Mild-moderate dysarthria – slurred words, but understandable (score 1)
Mute or severe dysarthria – unable to comprehend speech (score 2)
11 – Extinction: visual, tactile, auditory, or personal inattention to one side
No extinction noted (score 0)
Extinction to one extremity (score 1)
Profound unilateral extinction, more than one extremity or more than one modality (score 2)
Score is total out of 41 points

From Daniel Runde, MD. NIH Stroke Scale/Score (NIHSS) [Internet] 2016 [Accessed 2016 Mar 02]. Available at http://www.mdcalc.com/nih-stroke-scale-score-nihss/

major surgery at a non-compressible site, recent myocardial infarction or stroke, or recent or active major gastrointestinal or brain hemorrhage. All patients suspected of AIS above the age of 18 who present within 3 h of known symptoms onset (or last known well time) and have no bleeding or allergic contraindication should receive IV tPA, if feasible to give under that time target [1]. Systemic tPA is dosed at 0.9 mg/kg with 10 % of the dose given as an IV bolus and the remaining 90 % given over the course of an hour [1, 3]. A select group of AIS patients (those not on anticoagulation, younger than 80 years of age and without a previous diagnosis of both stroke and diabetes) continue to have a higher benefit/risk ratio from IV tPA to a 4.5 h time target [1, 4]. Patients taking the novel anticoagulants (Apixaban, Rivaroxiban, Dabigatran, Edoxaban) within the previous 2 days, patients on warfarin with an INR > 1.7 and patients on a therapeutic dose of IV heparin or subcutaneous low-molecular weight heparin should not receive IV tPA [1].

Table 35.2 Modified Rankin Score (can utilize the mRS-9Q scale [http://www.modifiedrankin.com/] for easy score determination)

Patient has no symptoms of any disease process at all (score 0)
Patient has mild symptoms of a disease, no disability, is independent (score 1)
Patient has mild – moderate symptoms of a disease, some disability, is independent (score 2)
Patient has moderate – severe symptoms of a disease, moderate disability, requires help with some activities of daily living, but is able to walk without assistance (score 3)
Patient has severe symptoms of a disease, with moderately severe disability and is unable to walk without assistance and is unable to attend to bodily needs without assistance (score 4)
Patient has severe symptoms of a disease, with severe disability, remains bedridden, incontinent and requires constant nursing care and attention (score 5)
Patient has died (score 6)

Acute Stroke Management, Endovascular Thrombectomy

Immediately following IV tPA administration, all AIS patients with known large cerebral vessel occlusion per imaging (CTA or MRA) should be considered for endovascular recanalization therapy [1, 5–7]. Several randomized controlled trials published in 2014 and 2015 (i.e. MR CLEAN, SWIFT PRIME, EXTEND IA, ESCAPE, REVASCAT) showed that endovascular therapy is indicated for select patients suffering acute ischemic stroke who present within 6 h of stroke onset (or last known well time) and meet certain imaging and clinical criteria [8–13]. Each of the studies showed a high likelihood of favorable outcome with a number needed to treat of 4 or less. The ideal patients considered for endovascular therapy should have an NIHSS score of greater than 6 and/or a severe deficit such as hemianopsia or aphasia, a CT ASPECTS of greater than 6 [14], a baseline independence of function (modified Rankin score of less than 2 (Table 35.2), show an acute perfusion abnormality to a brain territory, and have no contraindication to contrast-dye administration [6, 13]. Patients who benefited from endovascular therapy in the recent trials were those with a large anterior territory (anterior cerebral artery/middle cerebral artery/carotid terminus) artery occlusion who presented within the first hours of deficit, had an NIHSS score of >6, and were less than 80 years of age (Table 35.1) [8–12]. Patients with posterior territory strokes were not studied. The CT ASPECTS is calculated off of CT source images comparing the stroke-affected side with the unaffected side in 10 separate brain regions [15]. For each region noticeably affected, the ASPECTS is decreased from total score of 10 (no regions affected) to a score of zero (all regions affected).

Supportive Care

All AIS patients should ideally be monitored closely in a dedicated neurosciences ICU or in a stroke unit with continuous monitored telemetry and neurologic expertise for at least the first few days following an event. Patients under 60 years of age with large AIS (greater than 1/3 of a supratentorial hemisphere or a large cerebellar infarct) should be offered decompressive craniectomy within 48 h for definitive malignant cerebral

edema management before cerebral herniation occurs and without taking into account which hemisphere (dominant or non-dominant) has infarcted [1]. The DECIMAL, DESTINY and HAMLET studies show strong evidence for an improvement in outcome for patients under 60 years of age with large anterior circulation AIS who undergo early hemicraniectomy [16–18]. Outcomes of "medical optimization" of intracranial pressure with hyperosmolar agents (e.g. mannitol) prior to hemicraniectomy have not been readily studied, and delay of surgery while utilizing these therapies is not recommended [1]. At the time of this manuscript, there are ongoing studies examining whether medications such as IV glyburide for the management of malignant cerebral edema is efficacious in preventing the need for hemicraniectomy [19]. Physical, occupational and speech therapies should be offered to patients as soon as feasible [1]. All AIS patients should undergo a swallowing function examination upon admission and enteral access should be placed if the patient is unable to cooperate [1]. Daily delirium and depression screening and complication management (deep vein thrombosis prophylaxis, secondary pneumonia prevention, urinary tract infection reduction, etc.) is essential for successful outcome [1].

Atrial Fibrillation, Heart Failure and Anticoagulation

Several risk factors for the development of AIS have been identified. Although hypertension, hyperlipidemia, diabetes, vascular diseases and smoking history contribute significantly to one's stroke risk, atrial fibrillation is one of the most ubiquitous and greatest risk factors for stroke [20–22]. Recently, the CHA_2DS_2 -VASc scoring system was created and validated to stratify the yearly stroke risk in a patient with atrial fibrillation and compare it to the risk of bleeding from systemic anticoagulation (Table 35.3) [23]. Patients with a score higher than 2 are encouraged to start systemic anticoagulation so long as there are no additional contraindications or increased bleeding risks. Recently, novel anticoagulants (apixaban, edoxaban, dabigatran and rivaroxaban) have been FDA approved for use in patients with non-valvular atrial fibrillation. These novel oral anticoagulants (NOAC) were found to be superior to warfarin for stroke prevention in patients with atrial fibrillation with atrial fibrillation and in some cases (i.e. apixaban) with lower hemorrhage risk [24–27]. Patients with heart failure and an ejection fraction (EF) of <15 % are also at a higher risk for ischemic stroke. The WARCEF trial was completed which compared the efficacy of aspirin to warfarin in the prevention of heart failure related strokes [28, 29]. Among WARCEF patients with heart failure and EF of <15 % who were in sinus rhythm, there was no significant overall difference in the primary outcome between treatment with warfarin and treatment with aspirin.

Table 35.3 CHA_2DS_2 – VASc Score calculation for atrial fibrillation stroke risk

Congestive Heart Failure (score 1)
Hypertension - >140/90 (score 1)
Age > 75 years (score 2)
Diabetes mellitus (score 1)
Stroke, TIA or thromboembolism history (score 2)
Vascular disease (score 1)
Age 65 to 74 (score 1)
Sex **C**ategory– female gender (score 1)
Stroke risk/year in relation to score (off anticoagulation) is as follows:
Score 1: 1.3 % chance of stroke per year
Score 2: 2.2 % chance of stroke per year
Score 3: 3.2 % chance of stroke per year
Score 4: 4.0 % chance of stroke per year
Score 5: 6.7 % chance of stroke per year
Score 6: 9.8 % chance of stroke per year
Score 7: 9.6 % chance of stroke per year
Score 8: 6.7 % chance of stroke per year
Score 9: 15.2 % chance of stroke per year

Secondary Stroke Prevention in the Acute Stroke Setting

The SPARCL and JUPITER trials both found that certain HMG-CoA reductase inhibitors ("statins") reduce the risk of strokes and cardio-

vascular events in patients with recent stroke or transient ischemic attack [30–32]. The conclusion of the SPARCL trial was that high-dose atorvastatin 80 mg should be used; however there was a slight increase in the incidence of hemorrhagic stroke. Current recommendations state that patients with a concerning lipid panel (increased LDL, increased cholesterol, decreased HDL) should at least be started on a statin and the dose titrated to an improvement in lipid numbers over time. Regarding blood pressure, the long-term management strategy is to maintain systolic blood pressures less than 130 mmHg, however as is further described below, acute blood pressure management is as of yet controversial [1, 33–35]. Diabetes also should be controlled in a patient's long-term stroke management strategy, but clinicians should be careful to prevent hypoglycemia (glucose <60 mg/dL) and severe hyperglycemia (glucose >200 mg/dL) in the acute stroke setting [1, 36, 37]. ASA 81 mg with a single loading dose of 325 mg should also be started within 24–48 h of acute stroke as this was found to reduce rates of secondary stroke in both the CAST and IST studies [1, 38, 39]. Other antiplatelet agents such as clopidogrel and agents such as glycoprotein IIb/IIIa receptor antagonists have not been studied in acute secondary prevention of stroke, and their use is not currently recommended outside of clinical trials [1].

Evidence Contour

Several aspects of management in the patient with acute ischemic stroke remain without consensus in the face of available clinical trials.

"Wake-Up" Strokes

A number of patients (~25 % of all strokes) present to the emergency department with AIS symptoms noted only after awakening without knowledge of the exact time of onset [40]. In many of these patients the official "last-known well" time may have been several hours. There is some evidence to suggest that "wake-up strokes" may occur close to awakening and that these patients may also be tPA candidates, however the bleeding risk has not been assessed in this population. Clinical trials including WAKE-UP, SAIL-ON and EXTEND are ongoing to test the safety and efficacy of IV tPA on the wake-up stroke population.

Acute Cerebral Artery Dissection, Antiplatelets Versus Anticoagulation

Several studies have tried to address the question of whether anticoagulation or antiplatelet therapies are superior in the treatment of acute cerebral artery dissection. CADISS, a randomized controlled trial of 250 dissection patients (118 carotid, 132 vertebral) recently published in 2015 showed that there was no difference of efficacy between antiplatelet and anticoagulant medications at preventing the endpoints of stroke and death in those with symptomatic arterial dissection [41]. It should be noted however, that anticoagulant medications are associated with higher rates of both systemic and intracranial bleeding complications.

Blood Pressure Management in Acute Stroke Patients

Following AIS, the optimal blood pressure strategy was initially theorized to allow for permissive hypertension with a systolic goal of less than 180 to avoid countering the body's natural autoregulatory compensation of ischemia while minimizing secondary hemorrhagic complications. The large, randomized 2014 CATIS trial did not show a significant difference in patients who underwent aggressive blood pressure reduction (10–25 % within the first 24 h) to a goal of 140/90 within 7 days from the control group of patients in which they discontinued all antihypertensive medications [42]. Many stroke clinicians now opt for a lower target blood pressure as long as there are no symptomatic changes in the patient's neurological examination. Regarding exceptional conditions in which patients have symptomatic

hypotension that leads to neurological worsening ("perfusion dependence") there is some limited evidence that pharmacologically induced hypertension may be utilized for a short period under close monitoring [1]. There is however insufficient evidence to recommend volume expansion, prolonged pharmacologically induced hypertension, albumin infusions, and hemodilution for stroke patients.

Hemicraniectomy in Patients Older than 60 Years Old with Large Hemispheric Stroke

As previously discussed, several randomized control trials have shown a definite benefit in morbidity and mortality end-points to early hemicraniectomy for the reduction of malignant cerebral edema in patients under the age of 60 with large territory strokes within 24–48 h after onset of symptoms. DESTINY II a recent randomized trial showed that in patients over the age of 60, morbidity was marginally reduced by hemicraniectomy; however outcomes were complicated by significant morbidity [43]. Many of the patients who underwent hemicraniectomy in the trial improved only from a modified Rankin scale score of 6 (dead) to 5 (bed-bound with constant nursing care) and none of the patients in either arm became functionally independent. In the therapy of patients over the age of 60 with large stroke, the strategy to avoid mortality should largely center on medical therapy (osmotherapy) with family discussions on goals of care.

Early Rehabilitation in Stroke Patients

A number of hospital based studies, both in the ICU as well as on floor units have found that the early rehabilitation of patients is generally associated with better outcomes for patients across several pathologic processes, lower complication rates and fewer days spent in the hospital. The recent AVERT randomized controlled trial however showed that very early mobilization of AIS patients was associated with a reduction in the odds of a favorable outcome at 3 months and that early mobilization did not lead to fewer immobility related complications in these patients [44]. There was little to no harm caused by early mobilization and the study did not specifically speculate as to why there was a reduction in the favorable outcomes at 3 months. A number of stroke clinicians still advocate for early mobilization of stroke patients, as ongoing studies are pending. There is a randomized study published in 2011 utilizing Fluoxetine for motor recovery after acute ischemic stroke (FLAME study), which showed modest improvements in functional outcomes at 3 months post stroke in the Fluoxetine arm [45]. The mechanism for this improvement is unknown and it is speculated the medication may stimulate some degree of brain plasticity.

Basilar Artery Thrombosis, Therapy After 4.5 Hours

As with other strokes, if a patient arrives within the appropriate time window (<4.5 h) IV tPA should be initiated, if eligible, and the patient should be considered a candidate for endovascular therapy [1]. Basilar artery thrombosis is however an uncommon form of AIS and its consequences are often fatal [46]. There are a number of studies and case reports revealing improved outcomes following successful recanalization of the basilar artery even out to several hours post traditional timelines for anterior artery strokes, however due to the differences in management style and nature of these studies, recommendations regarding therapy are lacking. The prospectively collected BASICS registry indicates that about 1/3 of patients post recanalization with either IV tPA or intra-arterial therapy die, 1/3 lose functional independence and 1/3 regain function [47]. In general, for patients with limited symptomatology and suspected acute basilar occlusion, endovascular intervention may be warranted to limit the sequelae of the disease. The intra-arterial therapy can take place in some cases even up to 48 h post initial stroke symptoms with the potential for improved outcomes

[47]. Studies are ongoing to determine safety and efficacy of endovascular recanalization in posterior circulation large vessel strokes.

Endovascular Therapy Without IV tPA, After 4.5 Hours

IV tPA is limited in its utility after 4.5 h as the statistical risk of hemorrhage becomes greater than the potential benefit [48]. Endovascular therapy alone has not been shown to be inferior to IV tPA for the recanalization of vessels, and utilizing the newer stent-retriever devices has shown a greater than 90 % success rate in some studies [12, 13]. Due to the success rate of these devices and the lack of necessity to utilize tPA, some stroke clinicians and endovascular specialists offer intervention to 6 h or longer based on imaging criterion and clinical expertise. Some newer trials are utilizing the CT ASPECTS score and/or CT perfusion studies to calculate the risk and benefits of the procedure while others utilize MRI-DWI and penumbra characteristics to guide the decision for intra-arterial therapy [15]. The current recommendation for intra-arterial therapy without tPA is based on clinical examination and should be reserved for patients that either have a small ischemic core on MRI-DWI or an ASPECTS score >7 at the time of intervention [13].

Stenting in Acute Stroke Therapy

Intracranial arterial stenosis (ICAS) is generally caused by a buildup of plaques on the vessel walls and occurs in patients with atherosclerosis. When the stenosis becomes severe enough, it can lead to stroke either through plaque rupture or by occlusion of the vessel. The mainstay of therapy for patients with ICAS has been a combination of antiplatelet medications, anti-hypertensives, lipid-lowering agents, smoking cessation, lifestyle modification and diabetic glucose management. The SAMMPRIS trial, published in 2012 studied stenting versus aggressive medical therapy for ICAS [49]. Patients in both groups received dual anti-platelet medication with aspirin and clopidogrel for 90 days in addition to the modifications as listed above. The experimental arm additionally included endovascular stenting of a symptomatic cerebral artery. The study was halted early due to the high risk of stroke following stenting and because the risk of stroke with aggressive medical therapy alone was lower than expected. Patients with recurrent stroke due to ICAS despite aggressive medical therapy are now rarely offered intracranial stenting and it is recommended that these patients enroll in medical device trials.

Patients with extracranial arterial stenosis (ECAS) in the carotid arteries are candidates for either stenting or carotid endarterectomy [50–52]. The CREST trial published in 2010 addressed which therapeutic management was recommended for patients with ECAS [53]. It was found that patients had a higher risk of stroke with stenting and a higher risk of myocardial infarction with endarterectomy, and the composite primary outcome of stroke, myocardial infarction or death did not significantly differ between groups. Carotid artery stenting tended to show greater efficacy in patients under 70 years old, while carotid endarterectomy showed greater efficacy in those greater than 70 years old. CREST-2 is now currently in progress to assess the efficacy of stenting in asymptomatic patients [54].

Stenting for acute dissection has not been readily studied however can potentially provide some benefit in select patients who can tolerate a short course of dual-antiplatelet therapy.

Dual Anti-platelet Therapy, Aspirin plus Clopidogrel for Secondary Stroke Prevention

In 1996, the CAPRIE study, in 2005, the CARESS trial and in 2010 the CLAIR study showed that in patients with symptomatic carotid stenosis, combination therapy with clopidogrel and aspirin was more effective than aspirin alone in reducing asymptomatic embolization [55–57]. The MATCH trial, a 2004 study of 7599 patients, found that adding aspirin to clopidogrel in high risk patients with recent ischemic stroke or TIA

lead to greater bleeding risk than clopidogrel alone, and the combination was not associated with fewer ischemic events [58]. CHARISMA, a large 2006 study (15,603 patients), found that clopidogrel plus aspirin was not significantly more effective than aspirin alone in reducing the rate of myocardial infarction, stroke or death, and in 2012 the SPS3 study showed that the combination did not reduce the rate of lacunar stroke [59, 60]. A 2013 systematic review and meta-analysis later also found that dual-antiplatelet therapy lasting for more than 1 year did not reduce recurrent stroke risk and increased the risk for intracranial hemorrhage over clopidogrel monotherapy [61]. The CHANCE trial, also released in 2013, showed that among patients with TIA or minor stroke the treatment for the first 90 days with combination aspirin and clopidogrel followed by monotherapy reduced the risk of stroke and did not increase the risk of hemorrhage in the Chinese population [62]. A larger scale trial, POINT, is currently in progress to assess the efficacy and safety of short-term (90 day) dual-antiplatelet therapy [63]. In light of these studies, there is insufficient evidence to recommend long-term (>3 month) dual-antiplatelet therapy, however clinicians can consider short-term combination therapy for the treatment of recurrent stroke and micro-embolic events.

References

1. Jauch EC, Saver JL, Adams HP, et al. Guidelines for the early management of patients with acute ischemic stroke. Stroke. 2013;44:870–947.
2. Fonarow GC, Zhao X, et al. Door-to-needle times for tissue plasminogen activator administration and clinical outcomes in acute ischemic stroke before and after a quality improvement initiative. JAMA. 2014; 311(16):1632–40.
3. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med. 1995;333:1581–7.
4. Hacke W, Kaste M, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke (ECASS III). N Engl J Med. 2008;359:1317–29.
5. Furlan AJ, Higashida R, Wechsler L, Gent M, Rowley H, Kase C, et al. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. JAMA. 1999;282:2003–11.
6. Powers WJ, et al. 2015 American Heart Association/American Stroke Association Focused Update of the 2013 Guidelines for the Early Management of Patients with Acute Ischemic Stroke Regarding Endovascular Treatment: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2015;46(10):3020–35.
7. Addition of stent thrombectomy in treatment of acute ischemic stroke patients reduces disability in global studies [Internet] 2015. [Accessed 2 Mar 2016]. Available from http://www.businesswire.com/news/home/20150211006099/en/Addition-Stent-Thrombectomy-Treatment-Acute-Ischemic-Stroke.
8. Berkhemer OA, Fransen PS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke (MR CLEAN). N Engl J Med. 2015; 372(1):11–20.
9. Goyal M, Demchuk AM, Menon BK, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke (ESCAPE). N Engl J Med. 2015;372(11):1019–30.
10. Campbell BC, Mitchell PJ, Kleinig TJ, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection (EXTEND IA). N Engl J Med. 2015;372(11):1009–18.
11. Saver JL, Goyal M, Bonafe A, et al. Solitaire™ with the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke (SWIFT PRIME) trial: protocol for a randomized, controlled, multicenter study comparing the Solitaire revascularization device with IV tPA with IV tPA alone in acute ischemic stroke. Int J Stroke. 2015;10(3):439–48.
12. Jovin TG, Chamorro A, Cobo E, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke (REVASCAT). N Engl J Med. 2015;372(24):2296–306.
13. Broderick JP, Berkhemer OA, Palesch YY, et al. Endovascular therapy is effective and safe for patients with severe ischemic stroke: pooled analysis of interventional management of stroke III and multicenter randomized clinical trial of endovascular therapy for acute ischemic stroke in the Netherlands data. IMS III investigators; MR CLEAN Investigators. Stroke. 2015;46(12):3416–22.
14. Faculty of Medicine, University of Calgary. Understanding Alberta Stroke Program Early CT score (ASPECTS) [Internet] 2015 [Accessed 2 Mar 2016]. Available from: http://www.aspectsinstroke.com/aspects/what-is-aspects.
15. Hill MD, Demchuk AM, Goyal M. Alberta Stroke Program early computed tomography score to select patients for endovascular treatment: Interventional Management of Stroke (IMS)-III Trial. Stroke. 2014;45(2):444–9.
16. Hofmeijer J, Kappelle LJ, Algra A, Amelink GJ, van Gijn J, van der Worp HB, HAMLET investigators. Surgical decompression for space-occupying cerebral infarction (the Hemicraniectomy After Middle Cerebral Artery infarction with Life-threatening Edema Trial [HAMLET]): a multicentre, open, randomised trial. Lancet Neurol. 2009;8(4):326–33.
17. Jüttler E, Schwab S, Schmiedek P, Unterberg A, Hennerici M, Woitzik J, Witte S, Jenetzky E, Hacke W,

DESTINY Study Group. Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery (DESTINY): a randomized, controlled trial. Stroke. 2007;38(9):2518–25.
18. Vahedi K, Vicaut E, Mateo J, Kurtz A, Orabi M, Guichard JP, Boutron C, Couvreur G, Rouanet F, Touzé E, Guillon B, Carpentier A, Yelnik A, George B, Payen D, Bousser MG, DECIMAL Investigators. Sequential-design, multicenter, randomized, controlled trial of early decompressive craniectomy in malignant middle cerebral artery infarction (DECIMAL Trial). Stroke. 2007;38(9):2506–17.
19. Sheth KN, Elm JJ, Beslow LA, et al. Glyburide Advantage in Malignant Edema and Stroke (GAMES-RP) Trial: rationale and design. Neurocrit Care. 2016;24:132–9.
20. Paciaroni M, Agnelli G, Falocci N, et al. Prognostic value of trans-thoracic echocardiography in patients with acute stroke and atrial fibrillation: findings from the RAF study. J Neurol. 2016;263:231–7.
21. Mozaffarian D,Benjamin EJ, Go AS, et al. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics – 2015 update: a report from the American Heart Association. Circulation. 2015;131(4):e29–e322.
22. EAFT (European Atrial Fibrillation Trial) Study Group. Secondary prevention in non-rheumatic atrial brillation after transient ischaemic attack or minor stroke. Lancet. 1993;342(8882):1255–62.
23. Lip GY, Nieuwlaat R, Pisters R, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest. 2010;137(2):263–72.
24. Connolly SJ, Ezekowitz MD, Yusuf S, et al; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361(12):1139–51.
25. Granger CB, Alexander JH, McMurray JJ, et al; ARISTOTLE Commit- tees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365(11):981–92.
26. Patel MR, Mahaffey KW, Garg J, et al; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365(10):883–91.
27. Giugliano RP, Ruff CT, Braunwald E, et al; ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013;369(22):2093–104.
28. Homma S, Thompson JL, Pullicino PM, et al. Warfarin and aspirin in patients with heart failure and sinus rhythm (WARCEF). N Engl J Med. 2012;366(20):1859–69.
29. Pullicino PM, Qian M, Sacco RL, et al. Recurrent stroke in the warfarin versus aspirin in reduced cardiac ejection fraction (WARCEF) trial. Cerebrovasc Dis. 2014;38(3):176–81.
30. Amarenco P, Bogousslavsky J, Callahan A 3rd, et al; Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators. High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med. 2006;355(6):549–59.
31. Amarenco P, Benavente O, Goldstein LB, et al; Stroke Prevention by Aggressive Reduction in Cholesterol Levels Investiga- tors. Results of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial by stroke subtypes. Stroke. 2009;40(4):1405–9.
32. Ridker PM, Danielson E, Fonseca FAH, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein (JUPITER). N Engl J Med. 2008;359:2195–207.
33. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. Lancet. 2001;358(9287):1033–41.
34. Arauz-Pacheco C, Parrott MA, Raskin P, American Diabetes Association. Treatment of hypertension in adults with diabetes. Diabetes Care. 2003;26 Suppl 1:S80–2.
35. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ. 2009;338:b1665.
36. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008;359(15):1577–89.
37. Ray KK, Seshasai SR, Wijesuriya S, et al. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. Lancet. 2009;373(9677):1765–72.
38. CAST: randomised placebo-controlled trial of early aspirin use in 20,000 patients with acute ischaemic stroke. CAST (Chinese Acute Stroke Trial) Collaborative Group. Lancet. 1997;349(9066):1641–9.
39. The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. International Stroke Trial Collaborative Group. Lancet. 1997;349(9065):1569–81.
40. Rimmele DL, Thomalla G. Wake-up stroke: clinical characteristics, imaging findings, and treatment option – an update. Front Neurol. 2014;5:35.
41. Markus HS, Hayter E, Levi C, et al. Antiplatelet treatment compared with anticoagulation treatment for cervical artery dissection (CADISS): a randomised trial. Lancet Neurol. 2015;14(4):361–7.
42. He J, Zhang Y, Xu T, et al. Effects of immediate blood pressure reduction on death and major disability in patients with acute ischemic stroke: the CATIS randomized clinical trial. JAMA. 2014;311(5):479–89.
43. Jüttler E, Unterberg A, Woitzik J, et al. DESTINY II Investigators. Hemicraniectomy in older patients with extensive middle-cerebral-artery stroke. N Engl J Med. 2014;370(12):1091–100.
44. Bernhardt J, Langhorne P, Lindley RI, et al. Efficacy and safety of very early mobilisation within 24 h of

stroke onset (AVERT): a randomised controlled trial. Lancet. 2015;386(9988):46–55.
45. Chollet F, Tardy J, Albucher JF, et al. Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomised placebo-controlled trial. Lancet Neurol. 2011;10(2):123–30.
46. Baird TA, Muir KW, Bone I. Basilar artery occlusion. Neurocrit Care. 2004;1:319–29.
47. Schonewille WJ, Wijman CA, Michel P, et al. The basilar artery international cooperation study (BASICS). Int J Stroke. 2007;2(3):220–3.
48. The IST-3 Collaborative Group. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 hours of acute ischemic stroke (the third international stroke trial IST-3): a randomized controlled trial. Lancet. 2012;379(9834): 2352–63.
49. Derdeyn CP, Chimowitz MI, Lynn MJ, et al; Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis Trial Investigators. Aggressive medical treatment with or without stenting in high-risk patients with intracranial artery stenosis (SAMMPRIS): the Final results of a randomised trial. Lancet. 2014;383(9914):333–41.
50. North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis (NASCET). N Engl J Med. 1991;325(7):445–53.
51. Ferguson GG, Eliasziw M, Barr HW, et al. The North American Symptomatic Carotid Endarterectomy Trial: surgical results in 1415 patients. (NASCET). Stroke. 1999;30(9):1751–8.
52. International Carotid Stenting Study Investigators, Ederle J, Dobson J, et al. Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomised controlled trial. Lancet. 2010;375(9719):985–97.
53. Mantese VA, Timaran CH, Chiu D, et al. The Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST). Stroke. 2010;41:S31–4.
54. Brott TG. Carotid revascularization and medical management for asymptomatic carotid stenosis trial (CREST-2). In: ClinicalTrials.gov [website on the Internet]. Bethseda: US National Library of Medicine; 2014.
55. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. Lancet. 1996;348(9038):1329–39.
56. Markus HS, Droste DW, Kaps M, et al. Dual antiplatelet therapy with clopidogrel and aspirin in symptomatic carotid stenosis evaluated using doppler embolic signal detection: the Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) trial. Circulation. 2005;111(17):2233–40.
57. Wong KS, Chen C, Fu J, et al. Clopidogrel plus aspirin versus aspirin alone for reducing embolisation in patients with acute symptomatic cerebral or carotid artery stenosis (CLAIR study): a randomised, open-label, blinded-endpoint trial. Lancet Neurol. 2010;9(5):489–97.
58. Diener HC, Bogousslavsky J, Brass LM, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. Lancet. 2004;364(9431):331–7.
59. Bhatt DL, Fox KAA, Hacke W, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events (CHARISMA). N Engl J Med. 2006;354:1706–17.
60. SPS3 Investigators, Benavente OR, Hart RG, et al. Effects of clopidogrel added to aspirin in patients with recent lacunar stroke. N Engl J Med. 2012; 367(9):817–25.
61. Lee M, Saver JL, Hong KS, et al. Risk-benefit profile of long-term dual- versus single-antiplatelet therapy among patients with ischemic stroke: a systematic review and meta-analysis. Ann Intern Med. 2013;159(7):463.
62. Wang Y, Wang Y, Zhao X, et al; CHANCE Investigators. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. N Engl J Med. 2013;369(1):11–9.
63. Johnston SC, Easton JD, Farrant M, et al. Platelet-oriented inhibition in new TIA and minor ischemic stroke (POINT) trial: rationale and design. Int J Stroke. 2013;8(6):479–83.