ACUTE STROKE MANAGEMENT 2019 GUIDELINES:

SECONDARY PREVENTIVE TREATMENT:

ANTI-THROMBOTIC THERAPY (ANTIPLATELETS OR ANTICOAGULANTS):

Non-cardioembolic stroke:

- Aspirin is the first line preventive agents
- Dual antiplatelets (aspirin & clopidogrel):
  - Reasonable to use in mild stroke or TIA for 3 weeks (POINT and CHANCE shown more benefits than single agent with no increased risk of bleeding if used for 3 weeks)
  - Reasonable to use in patients with severe intracranial atherosclerosis > 70% for 90 days (SAMMPRIS trial)
- Recurrent stroke: -> evidence is controversial whether to switch to another agent or not (SPS3 found no benefit from switching to long-term dual antiplatelets, data analysis from aspirin failure patients in CHANCE and SOCRATES did show benefits from switching to an alternative therapy)

Side Note

- It would make sense to switch to dual antiplatelet therapy if patient had recurrent stroke on aspirin.
- Switching to clopidogrel? Many people have a loss of function variant of CYP2C9 (30% of European descent), which make clopidogrel is not as effective for use as single agent. Current studies are evaluating prasugrel and ticagrelor instead of clopidogrel for stroke prevention (not affected by CYP2C9 function).
- Increasing the dose of aspirin? It has shown non-beneficial. Theoretically doesn't help, aspirin inhibits thromboxane in both platelets (inhibiting platelet aggregation, irreversible) and in endothelial cells (promoting platelet aggregation by inhibiting prostacyclin, reversible), so then net effect is inhibition of platelet function due to irreversible effect on platelets compared with reversible effect on endothelial cells. Since a small dose aspirin is enough to inhibit platelets thromboxane, increasing the dose will just add inhibition of endothelial cells which promotes platelet aggregation.
- Consider anticoagulation? Reasonable. We used to wait for a hard proof evidence of cardioembolic stroke prior to starting warfarin, mainly to justify the bleeding risk of warfarin. Now, the bleeding risk from NOAGs is comparable with antiplatelet which makes it reasonable to switch to anticoagulation if cardioembolic stroke is suspected on brain imaging. An example would be a stroke bilateral ischemia in absence of aortic plaque. Cardioembolic stroke: everything has changed – BMJ 03/2018 – Dr. David Spencer

Cardioembolic stroke:

- **Recommended to use anticoagulation:** Atrial fibrillation, atrial flutter, MI with mural thrombus, mechanical cardiac valve or PFO with evidence of DVT
- **Reasonable to use anticoagulation:** Dilated cardiomyopathy EF < 35%, restrictive cardiomyopathy, acute STEMI without mural thrombus but with anterior or apical dyskinesia with EF < 40
- **Anticoagulation + Antiplatelets, reserved only for:**
  - Patients with atrial fibrillation with recent unstable coronary artery syndrome or coronary stenting (recommended)
  - Mechanical valve with stroke despite adequate anticoagulation (reasonable)
  - Bioprosthetic valve with stroke despite adequate antiplatelets (reasonable)
- **When to start**:
  - In most patients, it is reasonable to start anticoagulation between 4-14 days of onset.

- In patients with hemorrhagic transformation, if mild-moderate stroke with NIHSS < 9, restarting anticoagulation or antiplatelets within 14 days of onset was not associated with progression of HT. Individual assessment is warranted.

Side Note

- Patients at fall risk: usually benefits from anticoagulation will outweigh the risk of bleeding. Per Man-Son-Hing et al, it would take 295 falls to equal the risk of not taking anticoagulation in patients with atrial fibrillation.
- When anticoagulation seem contraindicated: in cases of recurrent intracerebral bleeding due to amyloid angiopathy or severe recurrent GI bleeding, occlusion of left atrial appendage should be considered.

Choosing antithrombotic therapy for elderly patients with atrial fibrillation who are at risk for falls – Dr. Man-Son

Hypercoagulable state stroke:

- **Recommended to use anticoagulation:** in patients with anti-phospholipid syndrome
- **Reasonable to use anticoagulation:** in patients with other inherited thrombophilia
- **Which anticoagulant to use:** warfarin is the anticoagulant that has been studied in thrombophilia

Summary of antithrombotic indications:

TREATMENT	INDICATIONS
ANTIPLATELETS	▪ First line preventive stroke therapy till work up is completed ▪ Non-cardioembolic stroke, presumed to be due to small vessel disease or large artery atherosclerosis
ANTICOAGULANTS	▪ Atrial fibrillation or flutter (recommended) ○ Anticoagulation should be restarted between 4-14 days after stroke onset in most patients. Patients with unstable angina or coronary artery stents, adding antiplatelets to anticoagulants may be warranted. ▪ Acute anterior STEMI without mural thrombus but with anterior or apical dyskinesia with EF < 40% (reasonable) ▪ MI with mural thrombus (recommended) ▪ Dilated cardiomyopathy with EF < 35% (reasonable) ▪ Restrictive cardiomyopathy (reasonable) ▪ Mechanical cardiac valve (recommended) ▪ PFO with evidence of DVT (recommended) ▪ Inherited thrombophilia state (reasonable) ▪ Antiphospholipid syndrome (recommended)
ANTIPLAETELETS + ANTICOAGULANTS	▪ Patients with atrial fibrillation with recent unstable coronary artery syndrome or coronary stenting (recommended) ▪ Mechanical valve with stroke despite adequate anticoagulation (reasonable) ▪ Bioprosthetic valve with stroke despite adequate antiplatelets (reasonable)
ANTIPLATELETS OR ANTICOAGULANTS	▪ For patients with extracranial carotid or vertebral dissection, treatment with either antiplatelet or anticoagulant is reasonable.

HYPERLIPIDEMIA TREATMENT:

- Patients below 75-year-old, high intensity statins should be instated with target >= 50% reduction of LDL-C
- Patients above 75-year-old, moderate or high intensity statins should be used
- Patients with high LDL-C (> 70 mg/dl) on maximum statin therapy, it is reasonable to add ezetimibe
- Women in childbearing age should be counseled to use contraception prior to using statins. Statins should be stopped 1-2 months prior to planned pregnancy.

Hypertension treatment:

Side Note

- It may be helpful to inform the patient that every 10mmHg reduction in systolic blood pressure was associated with 33% reduction in stroke risk *(Neal et al, Lancet 2000).*
- There may be protective effect of some antihypertensive medications (ACAE, ARB) even in patients with no concurrent hypertension, RR of 22% *(HOPE trial)*

CAROTID ARTERY STENOSIS:

- **CAS/CEA is recommended for:**
  - Symptomatic ICA stenosis > 50% by angio, MRA or CTA or > 70% by duplex and anticipated periprocedural risk of stroke < 6%.
  - Asymptomatic ICA stenosis > 70% by duplex (or > 60% by angio)
- **Medical management is recommended for:**
  - Symptomatic ICA stenosis after disabling stroke (mRS > 3)
  - Asymptomatic ICA stenosis 50-70%
- **CEA compared with CAS for ICA stenosis:**
  - CAS is generally preferred except in:
    - CEA is preferred in patients > 70-year-old (associated with improved outcome)
    - CEA is preferred in patients with unfavorable vascular anatomy for stenting.
  - CAS is particularly preferred in patients with increased risk for surgery, radiation induced stenosis or restenosis after prior CEA.
  - It is reasonable to perform procedure within 2 weeks of stroke onset if no contraindications
- Patients with minor non-disabling stroke (mRS 0-2), CEA or CAS should be done between 48h and 7 days of stroke onset.

- **OTHER ARTERIAL STNEOSIS**:
  - Severe intracranial stenosis with recurrent stroke despite adequate medical treatment (may be considered, SAMMPRIS trial)
  - Vertebral stenosis with recurrent stroke despite adequate medical treatment (may be considered)

Side Note

Medical management of ICA stenosis:

- For symptomatic ICA stenosis > 50%, medical management alone is not enough. NASCET trial showed 20-30% risk of recurrent stroke over 18 months period in medical treatment group.

- For non-intervention candidates (<50% stenosis), dual antiplatelets was not superior to single agent antiplatelet.
  - CHARISMA, MATCH and PROGESS trials showed that dual antiplatelet therapy was not superior to single antiplatelet agent in preventing stroke in ICA stenosis patients.
  - As usual, aspirin is preferred to clopidogrel due to genetic variability (CYP2C19 genetic variant is as common as 30% of European descents, preventing metabolism of clopidogrel to its active ingredient)

PFO CLOSURE:

- 2019 guidelines didn't comment on value or indications of PFO closure

Side Note

Patient selection for PFO closure: *Typically a younger patient with cryptogenic embolic stroke as detailed here.*

- Stroke: cortical infarcts, multiple vascular territories or strokes in same territories but of different ages. Negative workup, including at least 30-day monitoring for Afib.
- PFO: high risk PFO includes ASA, large shunt, large PFO > 2mm, increased atrial septal mobility
- Patient: RoPE score helps in patient selection, RoPE > 7 is usually associated with more favorable outcome.
  - RoPE score: 1 for each (no HTN, no DM, no hx of TIA/Stroke, non-smoker, cortical infarct) and age (5 points for 18-29, 4 for 30-39, 3 for 40-49, 2 for 50-59, 1 for 60-69 and 0 for > 70)
  - FDA mandates that patients be evaluated by both cardiologists and neurologists prior to the procedure.

Brief history of PFO closure approval:

- Amplatzer septal occlude was FDA approved in 2016 after RESPECT trial results showed superiority of PFO closure compared with medical therapy in cryptogenic stroke patients < 60-year-old.
- Cardioform septal occlude was FDA approved in 2018 after the REDUCE trial showed superiority of PFO closure compared with medical therapy in cryptogenic stroke patients < 60-year-old.
- CLOSE showed favorable results in patients with ASA or large Rt-Lt shunt (>30 bubbles in 3 cardiac cycles)
- DEFENSE-PFO showed favorable results in patients with ASA, PFO > 2mm or IAS hypermobility.

DISSECTION:

- Extracranial carotid or vertebral dissection: either antiplatelets or anticoagulants for 3-6 months
- Intracranial carotid or vertebral dissection: antiplatelet for 3-6 months
- Recurrent stroke in setting of extracranial dissection: the value of extracranial stenting is not well established

SUMMARY OF STROKE PREVENTION GUIDELINES

SITUATION	MANAGEMENT	EVIDENCE
Initial therapy	▪ Aspirin or aspirin/dipyridamole ▪ Clopidogrel is a reasonable alternative ▪ Dual antiplatelets (aspirin & clopidogrel) may be considered in small stroke or TIA for 21 days then monotherapy ▪ Long-term dual antiplatelet regimens are not recommended (increase risk of hemorrhage)	
Recurrent stroke/TIA while on aspirin	▪ Alternative antiplatelet may be considered although there is no enough studies available yet ▪ No evidence to support increasing dose of aspirin	
Symptomatic intracranial athero	▪ Dual antiplatelets for 90 days then monotherapy for stenosis > 70% ▪ Keep SBP < 140 mmHg ▪ Use high dose statins ▪ Wingspan stent is not recommended as initial management of intracranial stenosis	
Aortic arch atheroma	▪ Antiplatelets	
Symptomatic extracranial ICA stenosis	▪ CEA or CAS if > 70% stenosis by duplex or > 50% by angio	
Asymptomatic extracranial ICA stenosis	▪	
Dissection of extracranial ICA/vertebral	▪ Either antiplatelets or anticoagulation for 3-6 months ▪ Endovascular treatment may be considered in patients with recurrent storke/TIA despite medical management	
Atrial fibrillation	▪ Warfarin, apixaban or dabigatran are indicated for stroke prevention ▪ Rivaroxaban is reasonable alternative ▪ Combination of anticoagulation and antiplatelets for stroke prevention is not recommended. Can be used if indicated from cardiac prospective (acute coronary syndrome or stent placement) ▪ Aspirin is recommended for patients who can't tolerate anticoagulation ▪ After acute stroke, it is reasonable to initiate anticoagulation within 14 days of stroke onset unless there is high risk for hemorrhagic conversion, delaying beyond 14 days is reasonable.	

		▪ Bridging with LMWH is reasonable when temporary interruption of anticoagulation is needed. ▪ Usefulness of Watchman device is not certain
	MI with apical dyskinesia	▪ TIA or stroke in setting of acute anterior STEMI without mural thrombus but with anterior or apical dyskinesia with EF < 40% may be treated with warfarin for 3 months.
	MI with mural thrombus	▪ TIA or stroke in setting of acute MI with left ventricular mural thrombus should be treated with warfarin for 3 months. ▪ In patients who can't tolerate warfarin, apixaban, rivaroxaban, dabigatran or LMWH may be used.
	Cardiomyopathy	▪ TIA or stroke in setting of dilated cardiomyopathy (EF < 35%), restrictive cardiomyopathy or LVAD should be treated with warfarin.
	Rheumatic valvular heart disease	▪ Anticoagulation may be considered if no other cause for stroke
	Mitral valve prolapse	▪ Antiplatelets
	Mitral annular calcification	▪ Antiplatelets
	Mechanical mitral valve	▪ Anticoagulation with target 2-3 plus aspirin (add aspirin if low risk of bleeding) ▪ Addition of antiplatelet is recommended in patients with history of stroke prior to valve replacement ▪ Intensifying therapy with increasing INR or increasing aspirin to 325mg is reasonable in case of stroke despite adequate anticoagulation.
	Mechanical aortic valve	▪ Anticoagulation with target 2.5-3.5 plus aspirin (add aspirin if low risk of bleeding) ▪ Addition of antiplatelet is recommended in patients with history of stroke prior to valve replacement ▪ Intensifying therapy with increasing INR or increasing aspirin to 325mg is reasonable in case of stroke despite adequate anticoagulation.
	Bioprosthetic valve	▪ Antiplatelets (after the initial 6 month anticoagulation following valve placement). ▪ Adding warfarin with target INR 2-3 may be considered in case of stroke despite adequate antiplatelets
	PFO without DVT	▪ Antiplatelets ▪ No data to support PFO closure.

	PFO with DVT	▪ Anticoagulation, IVC filter if anticoagulation is contraindicated ▪ PFO closure may be considered if patient at risk of developing another DVT
	Inherited thrombophilia (protein C deficiency, protein S deficiency, antithrombin III deficiency, factor V Leiden, prothrombin G20210A mutation & MTHFR C677T mutation)	▪ Rarely involved in ischemic stroke in adults ▪ Anticoagulation may be considered depending on abnormality ▪ Long-term anticoagulation may be reasonable in case of cerebral venous thrombosis or recurrent ischemic stroke with evidence of thrombophilia
	Antiphospholipid Ab but not APL syndrome	▪ Antiplatelets
	Antiphospholipid syndrome	▪ Anticoagulation
	Sickle cell disease	▪ Chronic blood transfusion to keep HBS < 30%
	Pregnancy and anticoagulation	▪ Pregnancy with risk factor that require anticoagulation, use LMWH twice daily throughout pregnancy guided by Xa level drawn 4 hours after injection or LMWH for until the 13th week then warfarin till close delivery when LMWH is resumed.
	Pregnancy and antiplatelets	▪ Pregnancy with low risk factor that requires antiplatelets, either use LMWH or no treatment during first trimester
	Breastfeeding and anticoagulation	▪ Pregnancy with risk factor that require anticoagulation, use warfarin, LMWH or UFH
	Breastfeeding and antiplatelets	▪ Pregnancy with low risk factor that requires antiplatelets, low dose aspirin may be considered
	Resuming anticoagulation after ICH	▪ Low risk for stroke (AF without prior stroke) and high risk of ICH recurrence (elderly with lobar ICH) or poor neurological function, antiplatelet may be considered instead of anticoagulation. ▪ Optimal timing before restarting anticoagulation in patients with ICH, SAH or SDH who need restarting anticoagulation is uncertain but at least > 1 week.