

# 2022 Stroke Prevention Guidelines

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## Diagnostic Evaluation for secondary stroke prevention:

### Routine workup for all patients:

- Workup should be completed or underway within 48h of onset of stroke/TIA
- CT or MRI brain
- EKG
- CBC, PT, PTT, glucose, HbA1c, creatinine and lipid profile
- Vascular Imaging: Either carotid duplex or CTA/MRA head and neck. CTA/MRA can identify intracranial atherosclerotic disease, Moya Moya, dissection or other vasculopathies.

### Workup for ESUS:

- TEE, Cardiac CT or Cardiac MRI

### Patients with PFO:

- TCD with embolus detection may be reasonable to screen for Rt-Lt shunt

### Workup for Cryptogenic stroke:

- TTE with or without contrast
- Outpatient cardiac telemetry or implantable loop recorder
- Hypercoagulable panel
- Systemic inflammatory markers
- Screen for infections that can cause CNS vasculitis (HIV, syphilis)
- Drug screen (meth or cocaine)

## Vascular Risk Factor Management:

### Nutrition:

- Reasonable to advise patients to follow Mediterranean diet:
  - o Mono-unsaturated fat (use olive oil for cooking, consumption of tree nuts)
  - o Increase plant-based foods (fruit, vegetables, legumes, whole grains, cereals)
  - o Increase fish consumption
  - o Lower meat consumption, avoid red and processed meat
  - o Moderate milk and dietary consumption
  - o Avoid soda, pastries, sweets, bakery products
- Salt restriction to 2.5g/day in patients with HTN

### Physical activity:

- 10 minutes, 4 times weekly of moderate Intensity aerobic exercise or 20 minutes, twice weekly vigorous exercise

### Alcohol use:

- Counsel patients who drink >2 drinks/day for men or >1drink/day for women to reduce or eliminate alcohol consumption.

### Hypertension:

- BP goal of < 130/80 is recommended
- Thiazides, ACE or ARBs are useful for lowering BP and reducing stroke risk.

### Hyperlipidemia:

#### LDL:

- Start statins (atorvastatin 80) for stroke patients with LDL > 100 mg/dl if there is no other vascular risk factors, or LDL > 70 if known to have atherosclerotic disease (CAD, carotid disease, intracranial atherosclerosis).
- Add Ezetimibe if needed to get LDL < 70 mg/dl
- Add PCSK9 inhibitor (Repatha or Praluent) for very high risk patients with LDL > 70 mg/dl despite statins and ezetimibe.
  - o High risk patients are:
    - Stroke + (recent ACS, Hx of MI, sPAD) or
    - Multiple risk factors: Age > 65, HTN, DM, CKD, smokers, hx of CABG or prior cardiac stents
- Repeat fasting lipid profile after 4-12 weeks of therapy then every 3-12 months.

#### Triglycerides:

- Moderate hypertriglyceridemia (135-499) with LDL 40-100, HbA1c < 10 and no history of pancreatitis, AF or HF -> treatment with IPE (icosapent ethyl, Vascepa) 2g bid is reasonable
- Severe hypertriglyceridemia (> 500), fibrates can be used if necessary

### Diabetes:

- It is reasonable to screen for prediabetes/diabetes in ischemic stroke patients using HbA1c
- HbA1c target < 7 is recommended for most patients
- Prediabetic patients with BMI > 35 or those < 60 years of age or gestational diabetes, metformin may be beneficial to prevent progression to diabetes

## Antithrombotic therapy:

Patients with stroke/TIA not attributable to other etiology with specific antithrombotic recommendations:

- Aspirin, clopidogrel or aspirin 25 mg plus dipyridamole 200 mg bid is indicated for secondary prevention in non-cardioembolic stroke
- **DAPT (aspirin and clopidogrel)** should be initiated early (within 24h, maximum within 7 days) in patients with minor stroke (NIHSS  $\leq$ 3) or high risk TIA for 21 to 90 days followed by SAPT. *POINT trial*
- **DAPT (aspirin and ticagrelor)** for 30 days may be considered in patients with minor-moderate stroke (NIHSS  $\leq$ 5) or high-risk TIA or symptomatic intra or extracranial stenosis  $>$ 30%, although it may increase risk of serious bleeding. *THALES trial*
- **For patients already on aspirin** at time of non-cardioembolic stroke or TIA, effectiveness of increasing dose of aspirin or changing to clopidogrel is not well established.
- Continuous use of DAPT  $>$  90 days or the use of triple therapy in patients with non-cardioembolic stroke is associated with excess risk of hemorrhage.
- **Aspirin dosing** may be guided by weight: aspirin 75-100 in patients  $<$ 70kg and higher dose in patients  $>$ 70kg

### FYI:

*PROFESS*: no difference between aspirin-dipyridamole versus clopidogrel

*ESPRIT, ESPS2*: aspirin-dipyridamole was slightly more effective than aspirin alone

*CAPRIE*: found fewer events in clopidogrel group vs aspirin, but stroke events were the same

Aspirin

*POINT*: used 600mg clopidogrel load then 75mg daily and aspirin 50-325mg daily.

*CHANCE*: used 300 mg clopidogrel load and aspirin load of 75-300 then 75mg daily.

*THALES*: ticagrelor plus aspirin for 30 days reduced stroke recurrence vs aspirin alone (5% vs 6.3%) but increased serious bleeding risk (0.5% vs 0.1%)

## Management by Etiology:

### Intracranial Atherosclerosis:

#### Antiplatelets:

- Stroke/TIA caused by intracranial stenosis 50-99% -> **aspirin** 325 mg daily is recommended
- Stroke/TIA caused by intracranial stenosis 70-99% -> Adding **clopidogrel** to aspirin for 90 days is reasonable. (SAMMPRIS)
- Minor Stroke/TIA caused by intracranial stenosis > 30%, adding **ticagrelor** 90 mg bid to aspirin for 30 days can be considered
- Stroke/TIA caused by intracranial stenosis 50-99%, adding **cilostazol** 200mg/day to aspirin can be considered
- **Avoid:** clopidogrel, cilostazol or ticagrelor alone. Avoid aspirin + dipyridamole.

#### In Brief:

- Moderate intracranial stenosis: Either aspirin alone, aspirin + ticagrelor 90mg bid for 30 days or aspirin + cilostazol 200mg/d
- Severe intracranial stenosis: same as moderate plus one more option: aspirin + clopidogrel for 90 days

**Other measures:** maintain SBP < 140, high intensity statins and regular exercise

#### Angioplasty/Stenting:

- Avoid angioplasty/stenting prior to maximizing medical therapy first.
- Patients with recurrent symptoms despite the above, usefulness of angioplasty/stenting is unknown.

**Extracranial-intracranial bypass:** is not recommended

### Extracranial Carotid Stenosis:

#### Revascularization indication:

- Stroke/TIA with ipsilateral Carotid artery stenosis 70-99% -> CEA is recommended
- Stroke/TIA with ipsilateral Carotid artery stenosis 50-69% -> CEA is recommended

#### CEA vs CAS vs TCAR:

- **Patients > 70 years**, it is reasonable to select **CEA** over CAS to reduce periprocedural stroke rate
- If revascularization is planned **within 1 week** of index stroke, it is reasonable to select **CEA** over CAS to reduce periprocedural stroke rate
- Patients with severe stenosis with **increased risk for surgery** (medical risk, anatomic risk, radiation-induced stenosis), it is reasonable to select **CAS** over CEA.
- Patients with stenosis > 70% (non-invasive imaging) with low risk of periprocedural stroke, CAS can be considered as alternative to CEA.
- **TCAR** usefulness is uncertain

#### Timing:

- In patients with non-disabling stroke or TIA, it is reasonable to perform the procedure within 2 weeks of index event rather than delayed.

### Symptomatic Extracranial Vertebral Artery Stenosis:

- Main therapy is intensive medical management: antiplatelets, lipid lowering, BP control.
- Usefulness of stenting is not well established *VAST, VIST trials*
- Usefulness of open surgical procedures (endarterectomy, transposition) is not well established

## Aortic Arch Atherosclerosis:

- Target LDL < 60 mg/dl is recommended
- Antiplatelet therapy is recommended

### FYI:

High risk aortic arch plaque:  $\geq$  4mm thickness, ulcerated, mobile components or soft plaque without calcification. *FAPS trial*

2-year incidence of recurrent stroke in patients with no plaque is 10%, small plaque 16.5% and large plaque was 26.7%.

## Moya Moya Disease:

- Surgical revascularization with direct (STA-MCA) or indirect (encephaloduroarteriosynangiosis) bypass can be beneficial *JAM trial*
- Aspirin monotherapy may be reasonable

### FYI:

Moya Moya disease has bimodal age distribution, childhood (more ischemic) and adulthood (ischemic or hemorrhagic). Moya Moya syndrome is seen in patients with Down, sickle cell disease, neurofibromatosis and atherosclerosis.

## Small Vessel Disease:

- Antiplatelets (aspirin, clopidogrel) along with modifying risk factors
- Cilostazol usefulness in prevention of SVD stroke is still uncertain

### FYI:

CSPSII Japanese trial found Cilostazole is associated with less risk of ischemic or hemorrhagic stroke compared with aspirin. Cilostazol was associated with more side effects though (headache, dizziness, diarrhea, tachycardia). The study can't be generalized though due to being limited to one ethnic group and not duplicated.

## Atrial Fibrillation:

- **Anticoagulation** is recommended for stroke/TIA patients with nonvalvular AF (regardless if paroxysmal or persistent) or atrial flutter.
- **DOACs** (apixaban, rivaroxaban, dabigatran or edoxaban) are recommended in preference to warfarin in patients with no mechanical valve and no severe mitral stenosis.
- Patients with ESRD or on dialysis, use warfarin or apixaban,
- **Stroke with low risk of hemorrhagic conversion:** it is reasonable to initiate anticoagulation 2-14 days after onset.
- Stroke with high risk of hemorrhagic conversion (NIHSS > 9 or complete arterial territory): it is reasonable to delay initiation of anticoagulation beyond 14 days.
- If there is contraindication for lifelong anticoagulation but can tolerate at least 45 days, **Watchman** device closure of atrial appendage is reasonable.

### FYI:

**Left atrial appendage** is thought to be the main source of cardioembolism in AF. 90% of cardiac thrombi in patients with AF presenting with stroke were in left atrial appendage.

**DOACs vs Warfarin:** Warfarin reduced risk of stroke by 67% *SPAF*. Dabigatran was associated with lower risk of stroke compared to warfarin 1.11% versus 1.69% *RE-LY*. Rivaroxaban had similar risk of stroke/embolism to warfarin 2.1% vs 2.4% *ROCKET-AF*. Apixaban was superior to warfarin for stroke/embolism prevention 1.27% vs 1.6% and less bleeding 2.12% vs 3% *ARISTOTLE*. Edoxaban had similar rates to warfarin *ENGAGE AF-TIMI*. Overall DOACs had 19% reduction of stroke/embolism and 51% reduction in hemorrhagic stroke compared with warfarin.

**Atrial flutter** patients have similar risk of stroke, also 30% will develop atrial fibrillation within 2 years.

**Risk of stroke recurrence in setting of AF** is 1%/day. Risk of hemorrhagic conversion of stroke in patients with AF is 1-7% if tPA was not used, 6-21% if tPA is used.

**Watchman** similar stroke risk reduction to warfarin with less risk of bleeding. *PROTECT-AF, PREVAIL*. Watchman requires the use of anticoagulation for 45 days after procedure.

## Valvular Heart Disease:

AF with moderate or severe mitral stenosis or mechanical valve:

- **Warfarin** is recommended in patients with valvular AF.
- **Aspirin in addition to warfarin** is recommended to patients with mechanical mitral valve and a history of prior stroke/TIA before valve replacement.
- **Avoid dabigatran** in patients with stroke and mechanical heart valve.

Mechanical aortic valve:

- Warfarin with target INR of 2.5 is recommended for bileaflet or tilting disc valves.
- Higher intensity warfarin (2.5-3.5 *GELIA trial*) can be beneficial in patients with mechanical aortic valve with prior

IE patients with recurrent stroke and persistent vegetations despite antibiotics:

- Early surgery (before completion of AB course) is reasonable if there is no evidence of hemorrhagic conversion or extensive neurologic damage.
- Early surgery may be considered in patients with mobile vegetations > 10mm if there is no evidence of hemorrhagic conversion or extensive neurologic damage
- Delaying surgery for 4 weeks may be considered in patients with major ischemic stroke or intracranial hemorrhage.

### In Brief:

AF with severe mitral stenosis -> warfarin

Mechanical mitral valve -> warfarin

Mechanical mitral valve with prior hx of stroke/TIA -> warfarin + aspirin

Mechanical aortic valve -> warfarin target INR 2.5

Mechanical aortic valve with prior hx of stroke/TIA -> warfarin with INR of 3 or addition of aspirin to INR of 2.5

Prosthetic valve -> warfarin for 6 months then aspirin for life

IE with valvular vegetations and stroke > AB therapy first -> If recurrent stroke -> consider surgery if no extensive neurologic damage or intracranial hemorrhage.

### FYI:

**Bicuspid aortic valve, age related calcifications and Liebman Sacks endocarditis** are associated with increased risk of stroke, however there is no RCT for optimal therapy.

**Bioprosthetic valve:** Warfarin with target 2.5-3.5 is used for 3-6 months after bioprosthetic valve replacement followed by longterm aspirin only.

## LV Thrombus:

- Stroke/TIA with LV thrombus, warfarin for at least 3 months is recommended. Safety of DOACs is still uncertain.
- Stroke/TIA with acute MI, contrast TTE or cardiac MRI are reasonable to look for thrombus.
- Stroke/TIA with acute MI with reduced EF (< 50%), empirical anticoagulation for at least 3 months may be considered.

### FYI:

**Cardiac MRI** is more sensitive for LV thrombus detection in patients with acute STEMI.

**Incidence of LV thrombus in patients with anterior MI is 24%.** Incidence of stroke in patients with LV thrombus is 9%. Hence, empirical anticoagulation may be considered.

DOACs were associated with resolution of LV thrombus in 86% compared with 68% with warfarin in another study. However, embolic events were not studied with DOACs.

## Cardiomyopathy:

- **LV noncompaction** patients with stroke/TIA -> warfarin can be beneficial
- **Mechanical assist device (LVAD)** patients with stroke/TIA -> warfarin and aspirin can be beneficial. Dabigatran should be avoided, causes harm. So far, DOACs should be avoided in patients with LVAD.
- **Cardiomyopathy with reduced EF** but no AF and no LV thrombus -> effectiveness of anticoagulation vs antiplatelets is uncertain, treatment should be individualized.

### FYI:

Cardiomyopathy with low EF and sinus rhythm:

- **WARCEF**: no benefit of warfarin compared with aspirin over 3.5 years. Stroke incidence was less but hemorrhagic risks were higher.
- **COMMANDER HF**: no benefit of rivaroxaban 2.5mg in preventing stroke, MI, death. However, patients with prior stroke were underrepresented.

## PFO:

- **PFO closure is reasonable** in patients 18-60 year-old with ESUS and PFO **WITH** high risk anatomic features
- **PFO closure benefits are not well established** in patients 18-60 year-old with ESUS and PFO **WITHOUT** high risk anatomic features
- PFO closure should only rarely be performed in older patients (>60) and only in very unusual clinical circumstances.

### FYI:

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

- **Stroke features:** 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 features:** high risk PFO includes atrial septal aneurysm, large shunt (> 20 microbubble), large PFO > 2mm, increased atrial septal mobility > 10mm in either atrium
- **Patient features:** 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 atrial septal aneurysm 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.
- Meta analysis of all trials showed NNT to prevent a single stroke is 130 during 1 person-year or 13 for 10 person-year.
- PFO serious periprocedural complications rate is 4.9% in patients < 60 and 11% in patients >60.

## Dissection:

- Extracranial carotid or vertebral dissection, treatment with antithrombotic (aspirin or anticoagulation) for 3 months is indicated.
- Patients with recurrent stroke in setting of dissection despite antithrombotic, endovascular therapy may be considered.



**FYI:**

*CADISS* trial (cervical artery dissection in stroke study) found no significant difference in stroke incidence between aspirin and anticoagulation.

### Hypercoagulable state:

- PT20210 mutation, activated protein C resistance, elevated factor VIII, deficiency of protein C or S or antithrombin III:
  - o Antiplatelet therapy is reasonable
  - o Testing for protein C, S or antithrombin III should be done or repeated at least 4-6 weeks after acute stroke.
- Antiphospholipid syndrome:
  - o Isolated antiphospholipid Abs but doesn't fulfill the criteria -> antiplatelets (*WARSS* subgroup analysis)
  - o Fulfill the criteria for antiphospholipid -> warfarin
  - o Fulfill the criteria with triple positive Ab, rivaroxaban is NOT recommended

**FYI:**

Antiphospholipid syndrome diagnostic criteria: One clinical + One laboratory

**Clinical:** Vascular thrombosis or unexplained miscarriage (> 3 before 10<sup>th</sup> week or one after 10<sup>th</sup> week)

**Laboratory:** Positive lupus anticoagulant or medium/high titer anticardiolipin or high titer b2GP1 Ab. Labs test should be persistently positive after 12 weeks.

### Hyperhomocysteinemia:

- Vitamin B6, B12 and folate supplementation is not effective in preventing stroke in patients with stroke and Hyperhomocysteinemia *VITATOPOS trial*
- There is one study showed evidence of benefit of folic acid addition to enalapril in patients with Hyperhomocysteinemia and MTHFR mutation.

### Sickle Cell Disease:

- Chronic blood transfusion to keep HbS < 30% is recommended in patients with prior stroke/TIA and sickle cell disease *STOP trial*
- In patients for whom transfusion is not available, treatment with hydroxyurea is reasonable *SWITCH, TWITCH trials*

### Vasculitis:

#### Giant Cell Vasculitis:

- Immediate initiation of steroids is recommended in patients stroke/TIA attributed to GCA
- Methotrexate or tocilizumab therapy adjunctive to steroids is reasonable in these patients
- Infliximab shouldn't be used in stroke/TIA and GCA, it was associated with markers of disease activity and ocular symptoms.

#### Takayasu:

- Steroids plus methotrexate, azathioprine or leflunomide.

#### Primary CNS angiitis:

- High dose steroids followed by steroid sparing agents (azathioprine, cyclophosphamide, mycophenolate, methotrexate or rituximab).

#### Infectious vasculitis:

- VZV cerebral vasculitis, neurosyphilis or bacterial meningitis -> treat infectious etiology
- HIV vasculopathy -> aspirin in addition to HIV therapy

#### Neoplastic vasculitis (invasion of BVs by tumor cells)

- Angiotropic lymphoma is the most common neoplastic vasculitis, treat underlying lymphoma

## Other Genetic Disorders:

### Cystathionine B-synthase deficiency:

- Low methionine, cysteine-enhanced diet with supplementation with pyridoxine, B12 and folate is recommended to reduce plasma homocysteine level

### Anderson Fabry disease:

- Agalsidase alpha and beta are of uncertain value in preventing stroke.

## Carotid Web:

- Antiplatelets are recommended as first line in patients with carotid web in the distribution of stroke/TIA
- Carotid stenting/CEA may be considered in patients with ischemic stroke refractory to medical therapy

## Fibromuscular dysplasia:

- Antiplatelets, BP control are recommended for secondary stroke prevention
- Antiplatelets are recommended in patients with FMD and dissection with stroke/TIA
- Carotid angioplasty or stenting may be reasonable in patients with FMD with recurrent stroke.

## Dolichoectasia:

- Antiplatelet therapy or anticoagulation is reasonable in patients with stroke and dolichoectasia

## ESUS:

- Oral anticoagulants are not recommended for secondary stroke prevention
- Ticagrelor is not recommended for secondary stroke prevention
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### FYI:

*NAVIGATE ESUS* (rivaroxaban) and *RESPECT ESUS* (dabigatran) found no benefits of DOACs in patients with ESUS

*SOCRATES* showed no benefit of ticagrelor on recurrent vascular events