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Stroke State of the Art Treatment

Kevin M Barrett, MD
Professor & Chair
Department of Neurology
Mayo Clinic Florida

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DISCLOSURE OF RELEVANT FINANCIAL RELATIONSHIP(S) WITH INELIGIBLE COMPANIES

Kevin M. Barrett, M.D., faculty for this educational activity, has no relevant financial relationships with ineligible companies to disclose, and have indicated that the presentation or discussions will not include off-label or unapproved product.

All relevant financial relationships have been mitigated.

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LEARNING OBJECTIVES

- Understand the basis for adoption of *alternative thrombolytics* for treatment of acute ischemic stroke
- Choose evidence-based treatment strategies for *recent minor ischemic stroke & high-risk TIA*
- Implement effective and safe strategies for *secondary prevention* based on stroke mechanism

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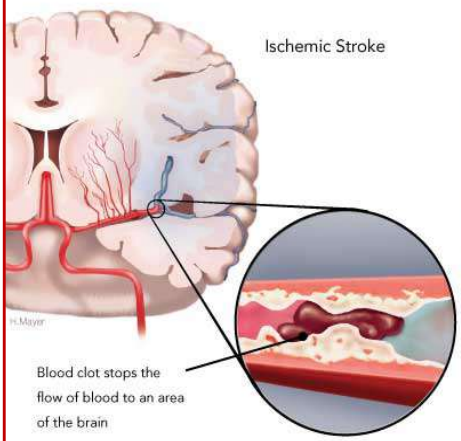
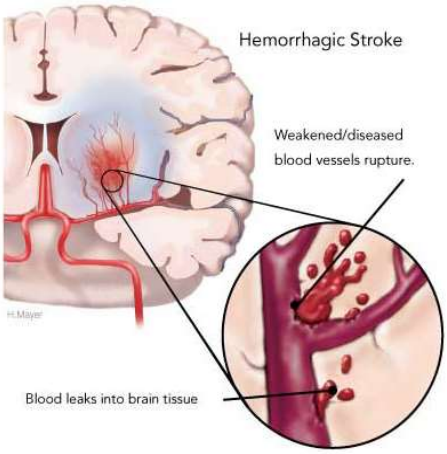
STROKE EPIDEMIOLOGY

STROKE SUBTYPES

Ischemic (85%)



Hemorrhagic (15%)



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Acute Stroke Treatment: Tenecteplase

- Tenecteplase (TNK): genetically modified variant of alteplase (ALT) to enhance affinity to clot-bound fibrin and extend duration of action
  - 14x specificity for fibrin
  - 80x resistance to plasminogen activator inhibitor (PAI-1)

Table I. Description of the molecular modifications in tenecteplase (TNK-tPA) compared to alteplase (t-PA), as depicted in figure 2

Designation	Amino acid substitution	Effect
T	Thr-103 →Asn	Adds a new glycosylation site on kringle-1, which decreases the rate of clearance but decreases fibrin binding
N	Asn-117→ Gln	Removes the existing glycosylation site on kringle-1, which decreases the rate of clearance and restores fibrin binding in combination with Thr-103 → Asn
K	Lys-His-Arg-Arg (296-299) → Ala-Ala-Ala-Ala	Increases fibrin specificity and makes the molecule more resistant to the naturally occurring inhibitor PAI-1

K = lysine; **N** = asparagine; **PAI** = plasminogen activator inhibitor; **T** = threonine.

- National Institute of Neurological Disorders S Study Group. *Tissue Plasminogen Activator for Acute Ischemic Stroke*. N Eng J Med 1995.
- European Cooperative Acute Stroke Study Investigators. *Thrombolysis with Alteplase 3 to 4.5 Hours after Acute Ischemic Stroke*. N Eng J Med 2008.

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Acute Stroke Treatment: Tenecteplase

- NOR-TEST (2017): TNK 0.4 mg/kg was noninferior nor superior to ALT 0.9 mg/kg
- EXTEND-IA TNK (2018): TNK 0.25 mg/kg vs ALT 0.9 mg/kg for patients with LVO showed 22% vs 10% recanalization rate at the time of initial catheter angiography
- Meta-analysis of 5 RCTs (2019) demonstrated TNK noninferiority to ALT at different doses
- 2019 American Heart/American Stroke Association guideline recognizes TNK as an alternative to TPA in patients with minor neurological impairment and large vessel occlusions

Burgos et al. Stroke. 2019;50:2156–62.

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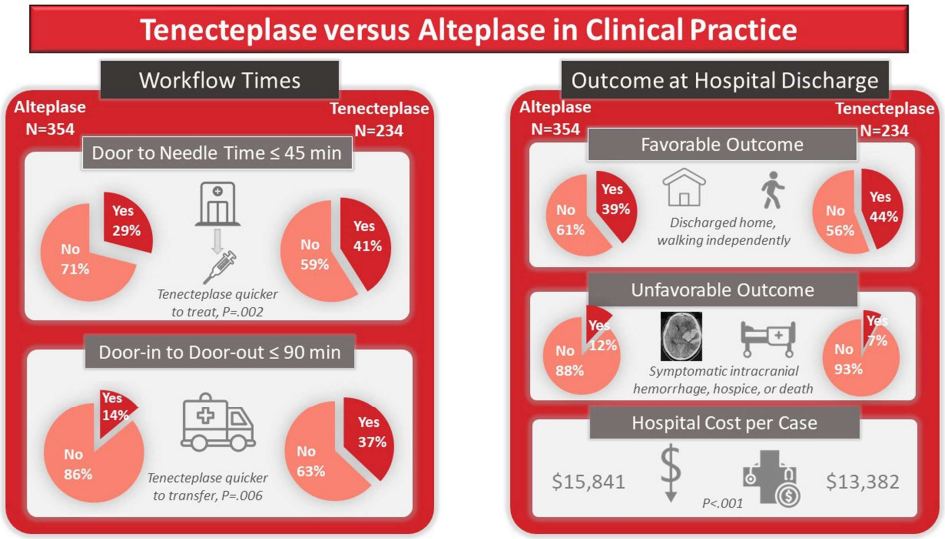

Warach et al. Stroke. 2022;53:3583–3593

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Antiplatelet Management
Non-cardioembolic Stroke/TIA

COR	RECOMMENDATIONS	
1	1. In patients with noncardioembolic ischemic stroke or TIA, antiplatelet therapy is indicated in preference to oral anticoagulation to reduce the risk of recurrent ischemic stroke and other cardiovascular events while minimizing the risk of bleeding	WARSS
1	2. For patients with noncardioembolic ischemic stroke or TIA, aspirin 50 to 325mg daily, clopidogrel 75mg, or the combination of aspirin 25mg and extended release dipyridamole 200mg twice daily is indicated for secondary prevention of ischemic stroke.	PRoFESS, ESPRIT, ESPS2, CAPRIE
1	3. For patients with recent minor (NIHSS ≤3) noncardioembolic ischemic stroke or high-risk TIA (ABCD^2 score ≥4), DAPT (aspirin plus clopidogrel) should be initiated early (ideally within 12-24 hours of symptom onset and at least within 7 days of onset) and continued for 21-90 days, followed by single antiplatelet therapy, to reduce the risk of recurrent ischemic stroke.	CHANCE, POINT
2b	4. For patients with recent (< 24 hours) minor to moderate stroke (NIHSS ≤5), or high-risk TIA (ABCD^2 score ≥6), or symptomatic intra- or extracranial ≥30% stenosis of an artery that could account for the event, DAPT with ticagrelor plus aspirin for 30 days may be considered to reduce the risk of 30-day recurrent stroke but may also increase the risk of serious bleeding events including ICH.	THALES
2b	5. For patients already taking aspirin at the time of noncardioembolic ischemic stroke or TIA, the effectiveness of increasing the dose of aspirin or changing to another antiplatelet medication is not well established.	
3 HARM	6. For patients with noncardioembolic ischemic stroke or TIA, the continuous use of DAPT (aspirin plus clopidogrel) for >90 days, or the use of triple antiplatelet therapy, are associated with excess risk of hemorrhage.	MATCH, SPS3; TARDIS

Kleindorfer D. *Stroke*. 2021;52:e364–e467.

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Dual Antiplatelet Therapy

	CHANCE (2013)	POINT (2018)
Inclusion	Stroke with NIHSS ≤3 or TIA with ABCD^2 score ≥4	Stroke with NIHSS ≤3 or TIA with ABCD^2 score ≥4
Intervention	Clopidogrel (300mg loading dose followed by 75mg daily) for 90 days plus aspirin (75mg daily) for 21 days	Clopidogrel (600mg loading dose followed by 75mg daily) for 90 days plus aspirin (50-325mg daily) for 90 days
Control	Placebo plus aspirin (75mg daily) for 90 days	Placebo plus aspirin (50-325mg daily) for 90 days
Primary Outcome	Stroke at 90 days: 8.2% in DAPT versus 11.7% in aspirin-only (p<0.001)	Ischemic stroke, MI, or vascular death: 5% in DAPT versus 6.5% in aspirin-only (p=0.02)
Major Hemorrhage	0.2% In DAPT versus 0.2% in aspirin-only (p=NS)	0.9% In DAPT versus 0.4% in aspirin-only (p=0.02)

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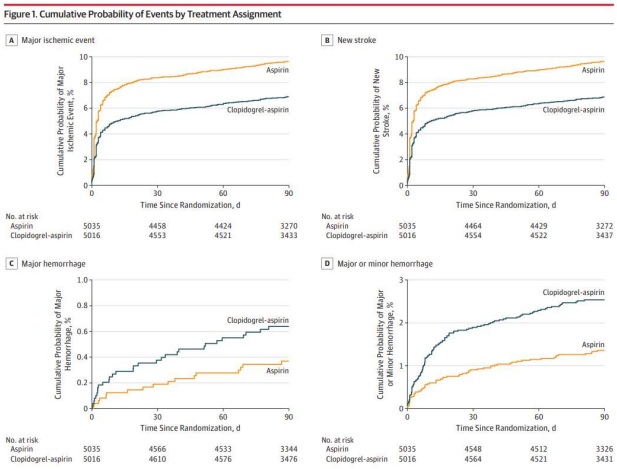
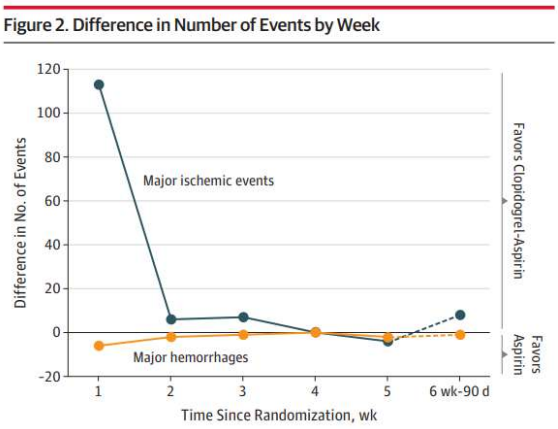
Dual Antiplatelet Therapy





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Pan et al. JAMA Neurol. 2019;76(12):1466-1473

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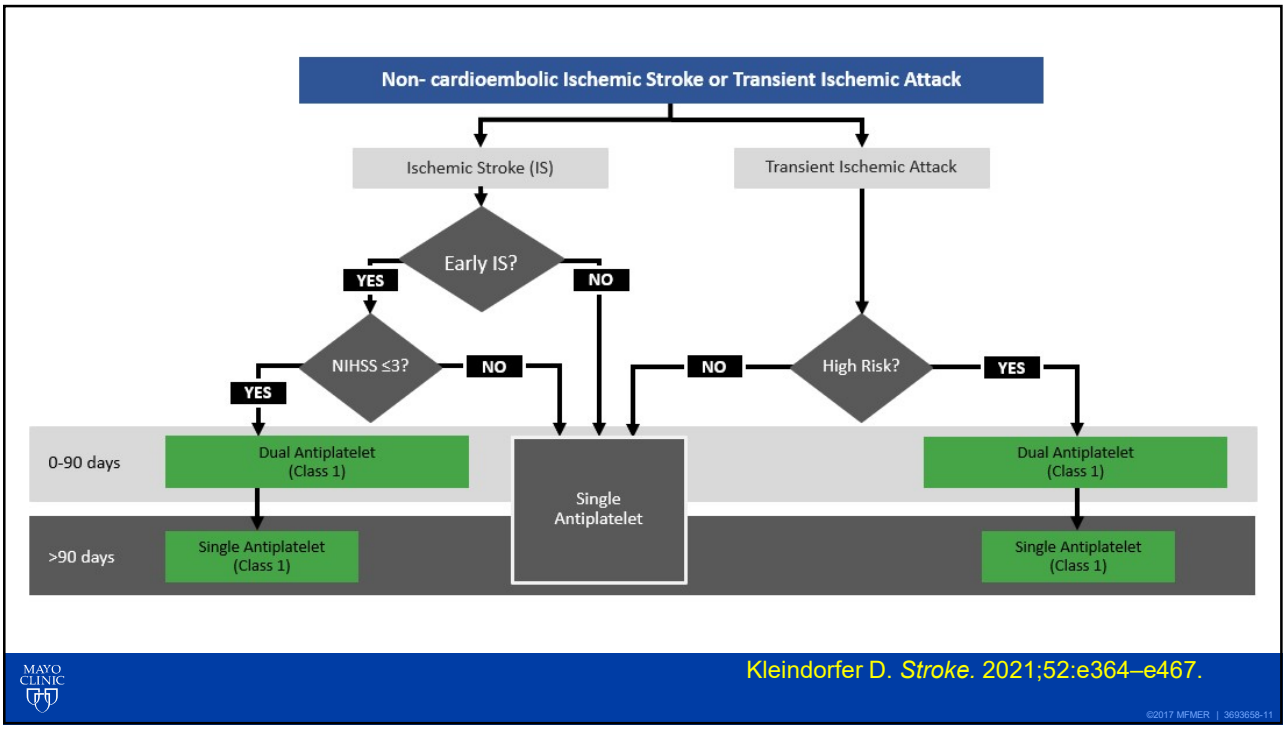

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SECONDARY STROKE PREVENTION

STROKE MECHANISMS

- 45-year-old Asian female
- PMH: HTN, HLD
- HPI: Episode of sudden onset left arm weakness lasting 2-3 minutes with complete resolution, then next day developed persistent left face and arm numbness and weakness
- Presents to ED for further evaluation
  - BP 185/110
  - CTH negative
- Admit for further evaluation

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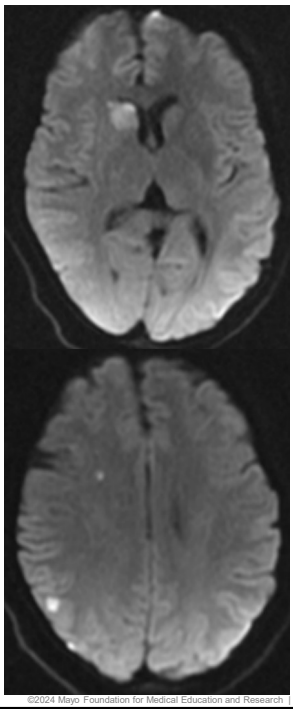
SECONDARY STROKE PREVENTION
STROKE MECHANISMS

- Evaluation:
  - MRI revealed multifocal right sided embolic appearing infarcts
  - Carotid ultrasound revealed no significant stenosis
  - TTE negative → TEE negative
  - HbA1c 5.5, total cholesterol 277, LDL 183
  - Thrombophilia evaluation negative
- Diagnosis: Cryptogenic stroke
- Treatment:
  - Started on ASA 81 mg and atorvastatin 80 mg
  - Loop recorder placed to eval for pAF



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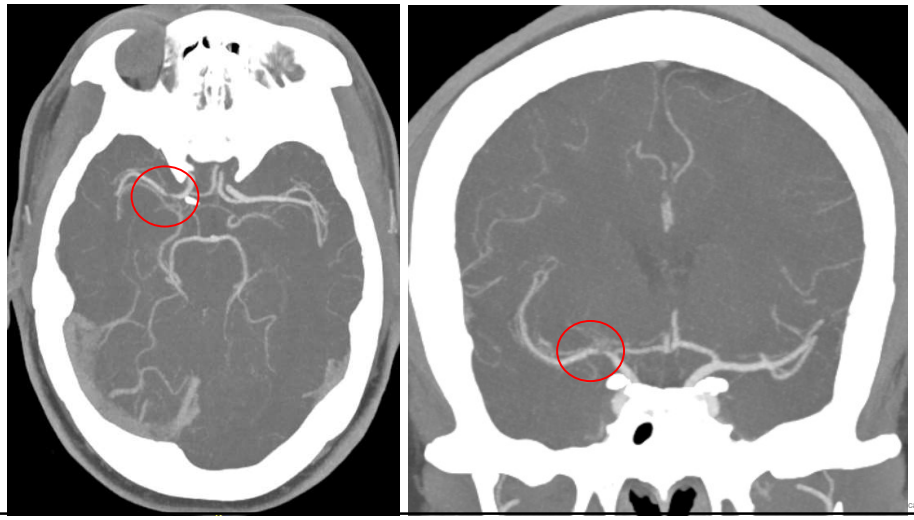
SECONDARY STROKE PREVENTION
STROKE MECHANISMS

- Presents to Mayo Clinic in July → CTA performed
- Diagnosis: symptomatic intracranial atherosclerosis



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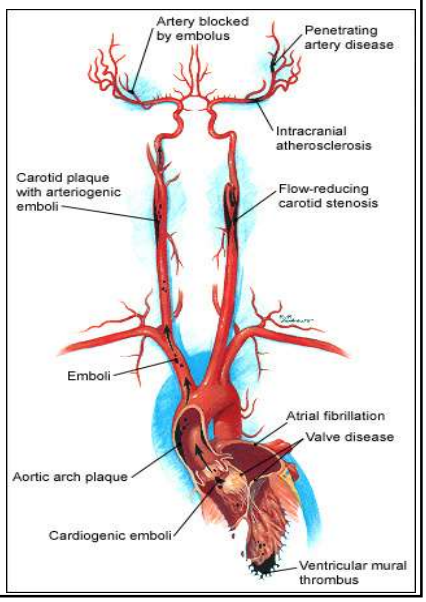
SECONDARY STROKE PREVENTION
STROKE MECHANISMS

- Cardioembolic (30%)
- Large vessel (15%)
- Small vessel (20%)
- Other known cause (dissection, thrombophilia, vasculopathy, etc) (5%)
- Cryptogenic (30%)



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SECONDARY STROKE PREVENTION
DIAGNOSTIC ALGORITHM

AHA/ASA GUIDELINE

2021 Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack

A Guideline From the American Heart Association/American Stroke Association

Reviewed for evidence-based integrity and endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons.

Endorsed by the Society of Vascular and Interventional Neurology

The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists.

Dawn O. Kleindorfer, MD, FAHA, Chair; Amytis Towfighi, MD, FAHA, Vice Chair; Seemant Chaturvedi, MD, FAHA; Kevin M. Cockroft, MD, MSc, FAHA; Jose Gutierrez, MD, MPH; Debbie Lombardi-Hill, BS, FAHA; Hooman Kamel, MD; Walter N. Kernan, MD*; Steven J. Kittner, MD, MPH, FAHA; Enrique C. Leira, MD, MS, FAHA; Olive Lennon, PhD; James F. Meschia, MD, FAHA; Thanh N. Nguyen, MD, FAHA; Peter M. Pollak, MD; Pasquale Santangeli, MD, PhD; Anjail Z. Sharrief, MD, MPH, FAHA; Sidney C. Smith Jr, MD, FAHA; Tanya N. Turan, MD, MS, FAHA†; Linda S. Williams, MD, FAHA

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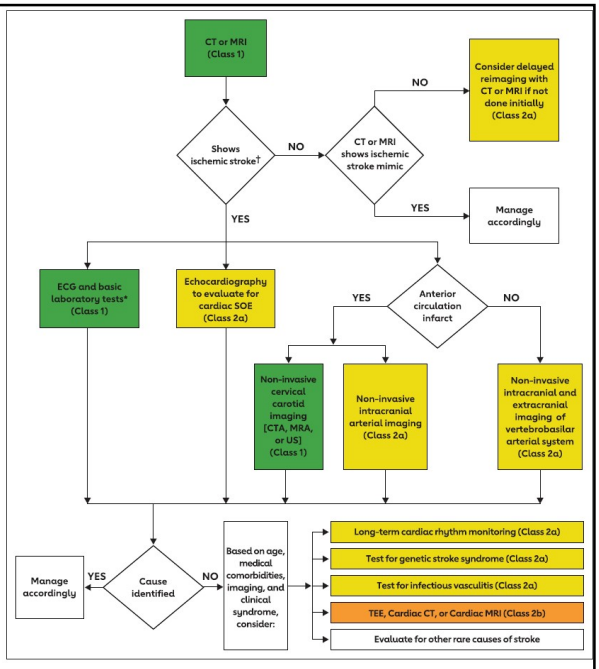
DIAGNOSTIC ALGORITHM

Outpatient Pearls

- MRI > CT as initial neuroimaging test
- Consider CTA or MRA head and neck instead of carotid ultrasound
- ECG and basic laboratory testing
  - CBC, PT/PTT, glucose, HbA1c, creatinine, lipid profile
- TTE with shunt study is good first line cardiac structural test



Kleindorfer D. *Stroke.* 2021;52:e364–e467

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SECONDARY STROKE PREVENTION

DIAGNOSTIC ALGORITHM

- Secondary prevention requires timely evaluation of stroke mechanism, with intent of identifying modifiable risk factors
  - Recurrent stroke risk varies markedly by stroke mechanism
- Cardiac imaging can detect indications for specific treatment including PFO, cardiac tumors, endocarditis, and intracardiac thrombi
- Long term cardiac monitoring in patients with cryptogenic stroke results in higher detection of atrial fibrillation
- Identification of symptomatic intracranial atherosclerosis supports treatment to aggressive antiatherosclerotic targets

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SECONDARY STROKE PREVENTION
MANAGEMENT BY ETIOLOGY

- Cardioembolism (30%)
  - More than 50% of cardioembolic strokes attributable to atrial fibrillation
  - NOAC is recommended in preference to warfarin in patients with nonvalvular AF
  - If patients have contraindication to lifelong NOAC and hx of nonvalvular AF, it may be reasonable to consider percutaneous closure of left atrial appendance with the Watchman device (Level 2b)

Recommendations for AF
Referenced studies that support recommendations are summarized in online Data Supplement 22.

COR	LOE	Recommendations
1	A	1. In patients with nonvalvular AF and stroke or TIA, oral anticoagulation (eg, apixaban, dabigatran, edoxaban, rivaroxaban, or warfarin) is recommended to reduce the risk of recurrent stroke.[419–426]
1	B-R	2. In patients with AF and stroke or TIA, oral anticoagulation is indicated to reduce the risk of recurrent stroke regardless of whether the AF pattern is paroxysmal, persistent, or permanent.[427]
1	B-R	3. In patients with stroke or TIA and AF who do not have moderate to severe mitral stenosis or a mechanical heart valve, apixaban, dabigatran, edoxaban, or rivaroxaban is recommended in preference to warfarin to reduce the risk of recurrent stroke.[419–426]
1	B-NR	4. In patients with atrial flutter and stroke or TIA, anticoagulant therapy similar to that in AF is indicated to reduce the risk of recurrent stroke.[427]
1	C-EO	5. In patients with AF and stroke or TIA, without moderate to severe mitral stenosis or a mechanical heart valve, who are unable to maintain a therapeutic INR level with warfarin, use of dabigatran, rivaroxaban, apixaban, or edoxaban is recommended to reduce the risk of recurrent stroke.

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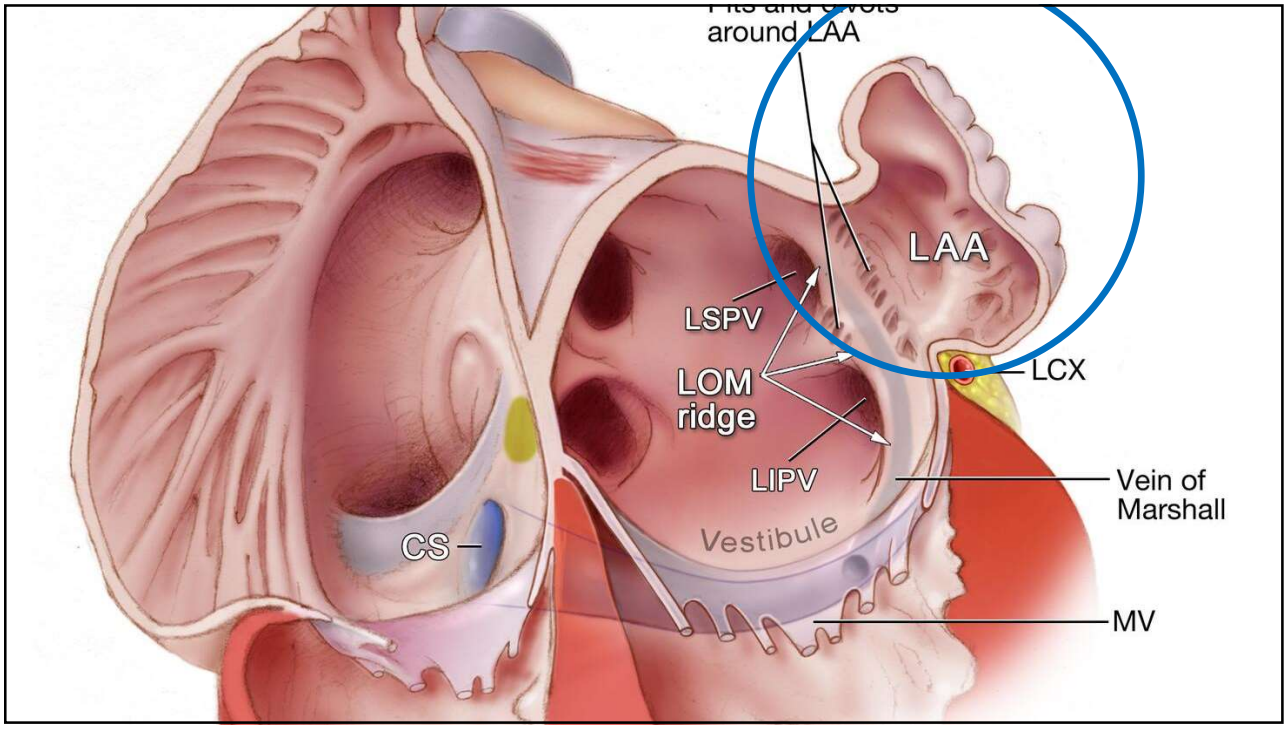

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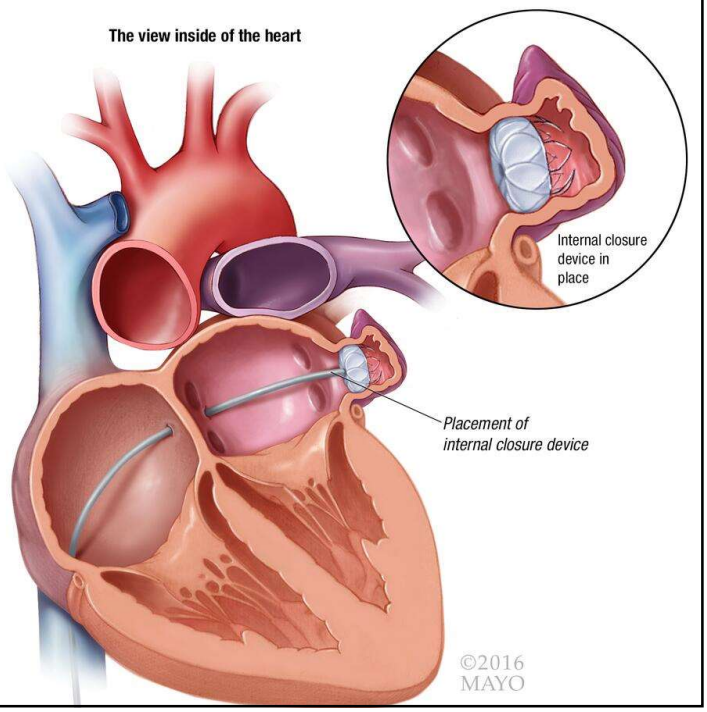
ATRIAL APPENDAGE CLOSURE

- PROTECT AF and PREVAIL trials compared warfarin to LAA closure with WATCHMAN device with subsequent warfarin discontinuation – overall showed net benefit to closure
- CHAMPION AF- currently underway comparing DOACs to LAA closure
- Post procedure-
  - 45 days of OAC + aspirin, then 4.5 months of DAPT
  - DAPT for 6 months



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SECONDARY STROKE PREVENTION
MANAGEMENT BY ETIOLOGY

- Large vessel disease (15%)
  - Intracranial atherosclerosis
  - Extracranial atherosclerosis
- Intracranial Atherosclerosis
  - Aspirin 325 mg indefinitely
  - Plavix 75 mg daily x 3 months
  - High intensity statin therapy
  - SBP < 140 mmHg
  - Moderate physical activity

Recommendations for Intracranial Large Artery Atherosclerosis
Referenced studies that support recommendations are summarized in online Data Supplements 20–22.

COR	LOE	Recommendations
		Antithrombotic Therapy
1	B-R	1. In patients with a stroke or TIA caused by 50% to 99% stenosis of a major intracranial artery, aspirin 325 mg/d is recommended in preference to warfarin to reduce the risk of recurrent ischemic stroke and vascular death.[335,336]
2a	B-NR	2. In patients with recent stroke or TIA (within 30 days) attributable to severe stenosis (70%–99%) of a major intracranial artery, the addition of clopidogrel 75 mg/d to aspirin for up to 90 days is reasonable to further reduce recurrent stroke risk.[336–339]
		Risk Factor Management
1	B-NR	6. In patients with a stroke or TIA attributable to 50% to 99% stenosis of a major intracranial artery, maintenance of SBP below 140 mm Hg, high-intensity statin therapy, and at least moderate physical activity are recommended to prevent recurrent stroke and vascular events.[110,210,337,345–349]

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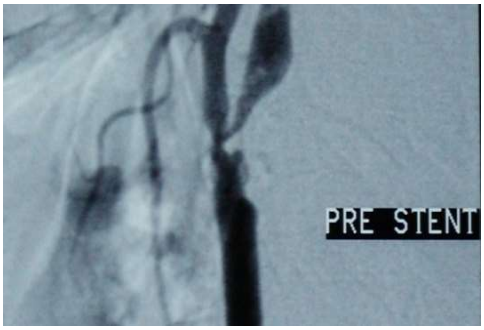
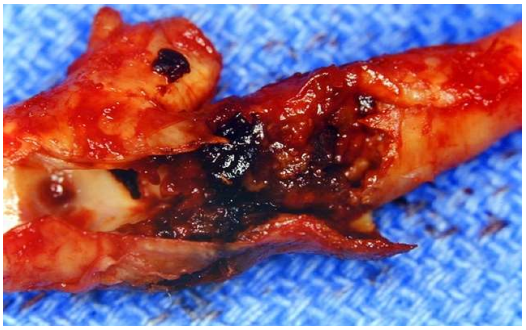
CAROTID DISEASE

- Associated with 5-8% of ischemic strokes in 2017, compared to 30% in 1980
- And since 2003, stroke mortality has declined an astounding 41%





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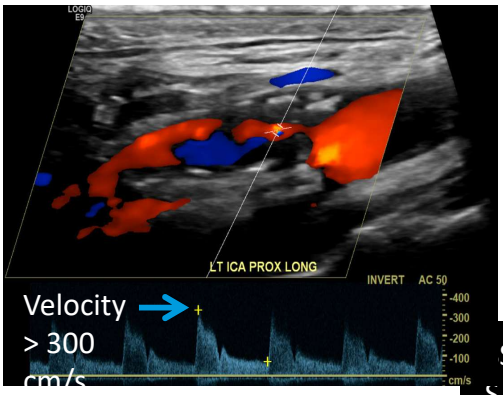

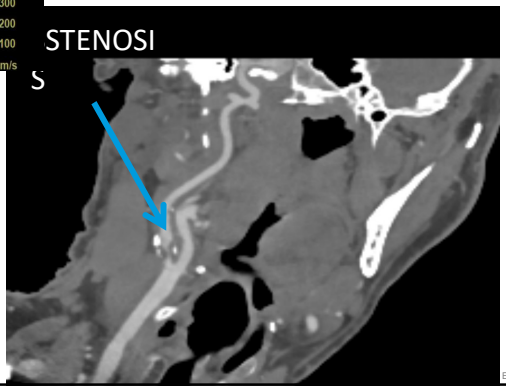

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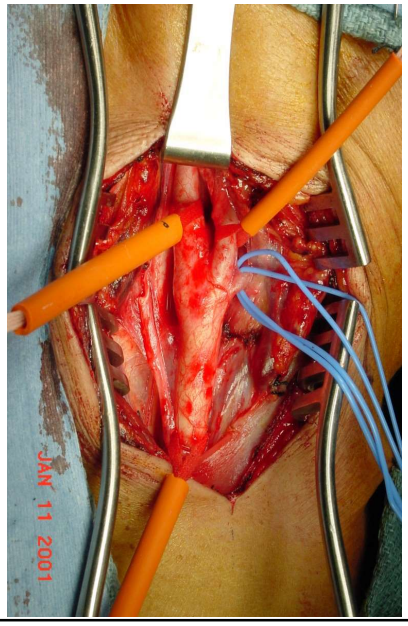
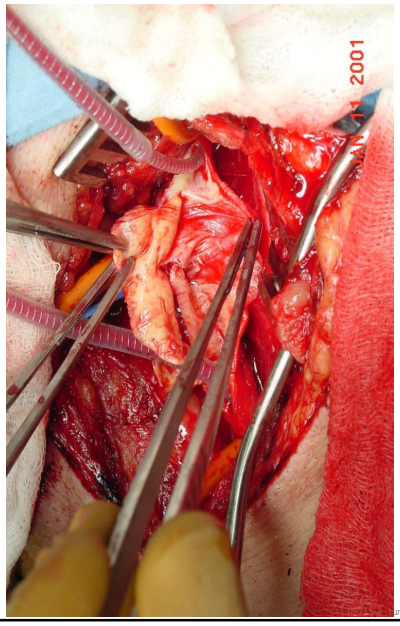
CAROTID ENDARTERECTOMY (CEA)





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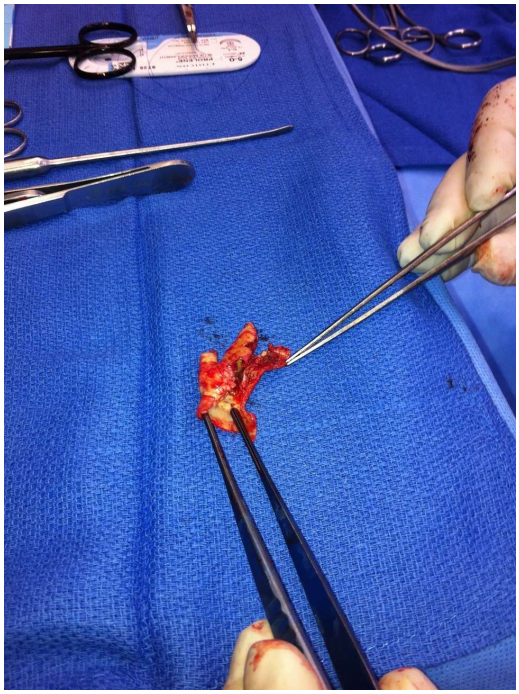

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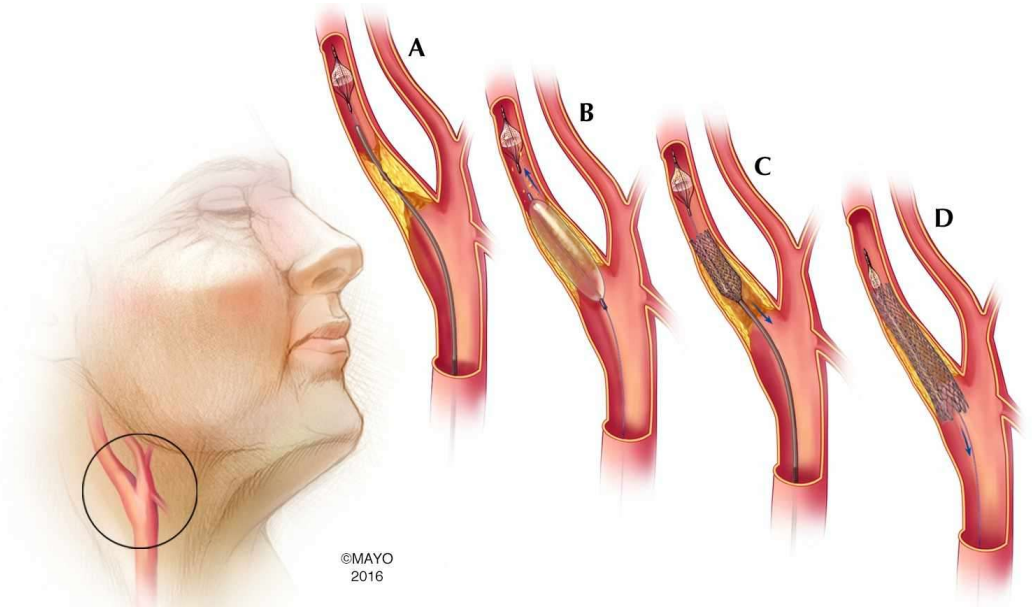
Carotid Angioplasty & Stenting (CAS)



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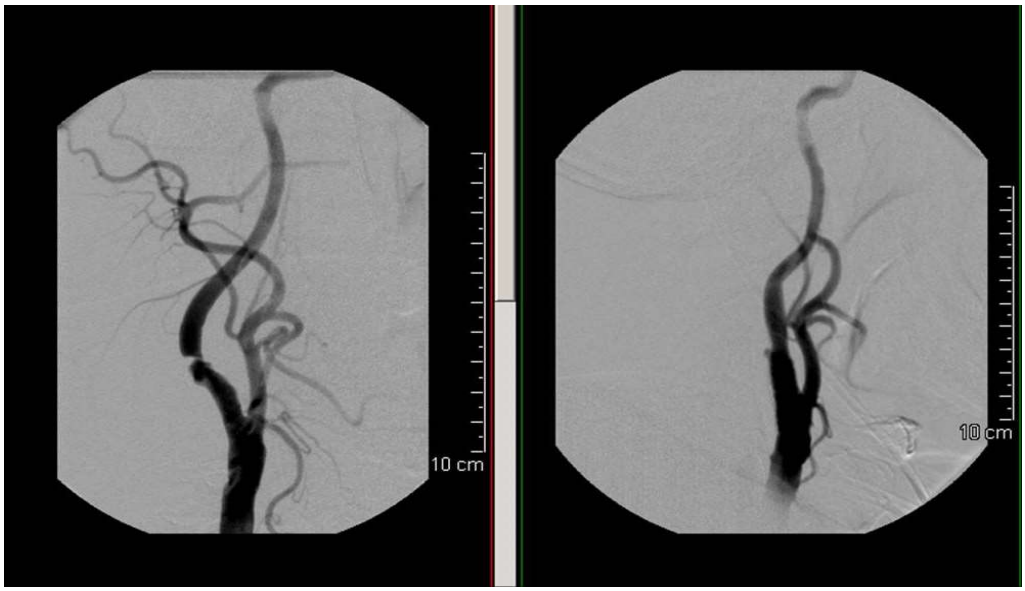
CAROTID ANGIOPLASTY & STENTING (CAS)



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TCAR: TRANSCAROTID ARTERY REVASCULARIZATION

- Transfemoral carotid artery stenting has not surpassed performance of CEA on average
- CREST and other trials have found higher periprocedural stroke rates with TF CAS
- TCAR is a hybrid technique based on temporary occlusion of CCA with reversal of flow in the CCA, ECA, and ICA.
- TCAR avoids endovascular manipulation within aortic arch via surgical CCA access and provides flow reversal before manipulation of lesion and throughout stenting procedure.

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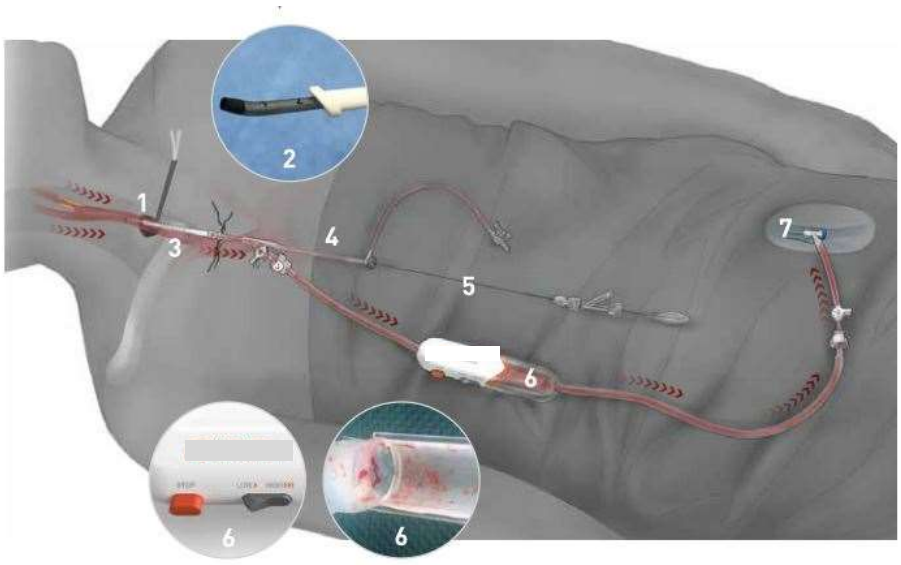
TCAR: TRANSCAROTID ARTERY REVASCULARIZATION



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SECONDARY STROKE PREVENTION
MANAGEMENT BY ETIOLOGY

- Symptomatic Carotid Stenosis
  - Revascularization considered in patients with stroke or TIA in last 6 months and:
    - Ipsilateral severe (70-99%) stenosis (Level IA)
    - Ipsilateral moderate (50-69%) stenosis (Level 1B)
  - In patients ≥ 70 yo, CEA is reasonable to select over CAS to reduce periprocedural risk (Level 2a)
  - Intensive medical therapy (antiplatelet therapy, high intensity statin, and treatment of hypertension)

Recommendations for Extracranial Carotid Stenosis
Referenced studies that support recommendations are summarized in online Data Supplement 28.

COR	LOE	Recommendations
1	A	1. In patients with a TIA or nondisabling ischemic stroke within the past 6 months and ipsilateral severe (70%–99%) carotid artery stenosis, carotid endarterectomy (CEA) is recommended to reduce the risk of future stroke, provided that perioperative morbidity and mortality risk is estimated to be <6%.[369]
1	A	2. In patients with ischemic stroke or TIA and symptomatic extracranial carotid stenosis who are scheduled for carotid artery stenting (CAS) or CEA, procedures should be performed by operators with established periprocedural stroke and mortality rates of <6% to reduce the risk of surgical adverse events.[370]
1	A	3. In patients with carotid artery stenosis and a TIA or stroke, intensive medical therapy, with antiplatelet therapy, lipid-lowering therapy, and treatment of hypertension, is recommended to reduce stroke risk.[210]
1	B-R	4. In patients with recent TIA or ischemic stroke and ipsilateral moderate (50%–69%) carotid stenosis as documented by catheter-based imaging or noninvasive imaging, CEA is recommended to reduce the risk of future stroke, depending on patient-specific factors such as age, sex, and comorbidities, if the perioperative morbidity and mortality risk is estimated to be <6%.[369]

Kleindorfer D. *Stroke*. 2021;52:e364–e467

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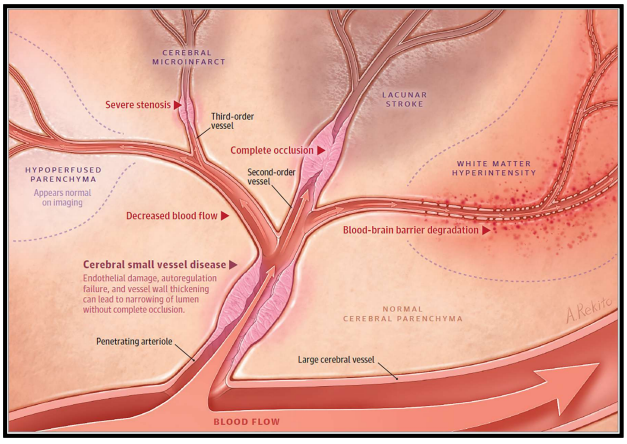
SECONDARY STROKE PREVENTION
MANAGEMENT BY ETIOLOGY

- Small Vessel Disease (20%)
  - Single agent antiplatelet
    - Role of cilostazol remains uncertain
  - SBP target < 130 mmHg
  - Target HbA1c < 7%
  - Target LDL < 70 mg/DL
  - Smoking cessation



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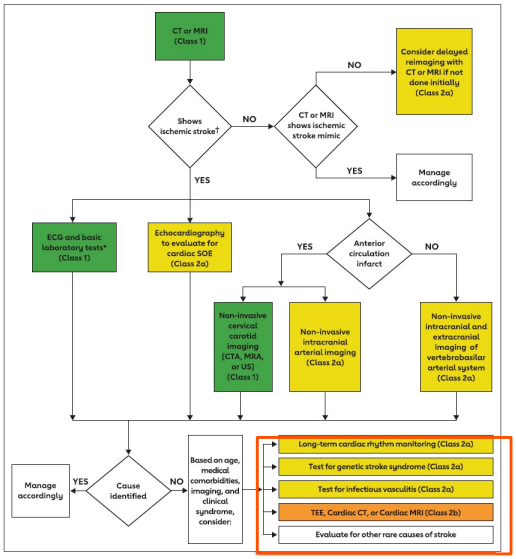
SECONDARY STROKE PREVENTION

MANAGEMENT BY ETIOLOGY

- Cryptogenic Stroke (30%)
  - Antiplatelet and statin therapy pending further evaluation
  - Consider specific testing on individual basis
    - Long-term cardiac monitor
    - Genetic testing
    - Vasculitis (LP, serology, etc)
    - Cardiac structural testing



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Antiplatelet Management

Non-cardioembolic Stroke/TIA

COR	RECOMMENDATIONS	
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1	2. For patients with noncardioembolic ischemic stroke or TIA, aspirin 50 to 325mg daily, clopidogrel 75mg, or the combination of aspirin 25mg and extended release dipyridamole 200mg twice daily is indicated for secondary prevention of ischemic stroke.	PRoFESS, ESPRIT, ESPS2, CAPRIE
1	3. For patients with recent minor (NIHSS ≤3) noncardioembolic ischemic stroke or high-risk TIA (ABCD^2 score ≥4), DAPT (aspirin plus clopidogrel) should be initiated early (ideally within 12-24 hours of symptom onset and at least within 7 days of onset) and continued for 21-90 days, followed by single antiplatelet therapy, to reduce the risk of recurrent ischemic stroke.	CHANCE, POINT
2b	4. For patients with recent (< 24 hours) minor to moderate stroke (NIHSS ≤5), or high-risk TIA (ABCD^2 score ≥6), or symptomatic intra- or extracranial ≥30% stenosis of an artery that could account for the event, DAPT with ticagrelor plus aspirin for 30 days may be considered to reduce the risk of 30-day recurrent stroke but may also increase the risk of serious bleeding events including ICH.	THALES
2b	5. For patients already taking aspirin at the time of noncardioembolic ischemic stroke or TIA, the effectiveness of increasing the dose of aspirin or changing to another antiplatelet medication is not well established.	
3 HARM	6. For patients with noncardioembolic ischemic stroke or TIA, the continuous use of DAPT (aspirin plus clopidogrel) for >90 days, or the use of triple antiplatelet therapy, are associated with excess risk of hemorrhage.	MATCH, SPS3; TARDIS

MAYO CLINIC

Kleindorfer D. *Stroke*. 2021;52:e364–e467.

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Antiplatelet Management
Non-cardioembolic Stroke/TIA

COR	RECOMMENDATIONS	
1	1. In patients with noncardioembolic ischemic stroke or TIA, antiplatelet therapy is indicated in preference to oral anticoagulation to reduce the risk of recurrent ischemic stroke and other cardiovascular events while minimizing the risk of bleeding	WARSS
1	2. For patients with noncardioembolic ischemic stroke or TIA, aspirin 50 to 325mg daily, clopidogrel 75mg, or the combination of aspirin 25mg and extended release dipyridamole 200mg twice daily is indicated for secondary prevention of ischemic stroke.	PRoFESS, ESPRIT, ESPS2, CAPRIE
1	3. For patients with recent minor (NIHSS ≤3) noncardioembolic ischemic stroke or high-risk TIA (ABCD^2 score ≥4), DAPT (aspirin plus clopidogrel) should be initiated early (ideally within 12-24 hours of symptom onset and at least within 7 days of onset) and continued for 21-90 days, followed by single antiplatelet therapy, to reduce the risk of recurrent ischemic stroke.	CHANCE, POINT
2b	4. For patients with recent (< 24 hours) minor to moderate stroke (NIHSS ≤5), or high-risk TIA (ABCD^2 score ≥6), or symptomatic intra- or extracranial ≥30% stenosis of an artery that could account for the event, DAPT with ticagrelor plus aspirin for 30 days may be considered to reduce the risk of 30-day recurrent stroke but may also increase the risk of serious bleeding events including ICH.	THALES
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3 HARM	6. For patients with noncardioembolic ischemic stroke or TIA, the continuous use of DAPT (aspirin plus clopidogrel) for >90 days, or the use of triple antiplatelet therapy, are associated with excess risk of hemorrhage.	MATCH, SPS3; TARDIS

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TAKE HOME MESSAGE/ NEXT STEPS

- Tenecteplase has been adopted as the thrombolytic of choice in most stroke centers for treatment of acute ischemic stroke
- Selected patients with recent minor ischemic stroke/high risk TIA should be treated with dual antiplatelet therapy
- Characterization of stroke mechanism informs evidence-based approach to stroke prevention

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