THE WARREN ALPERT
Medical School
BROWN UNIVERSITY

Rhode Island STROKE SYMPOSIUM

Antiplatelets for stroke prevention in a nutshell

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DISCLOSURE

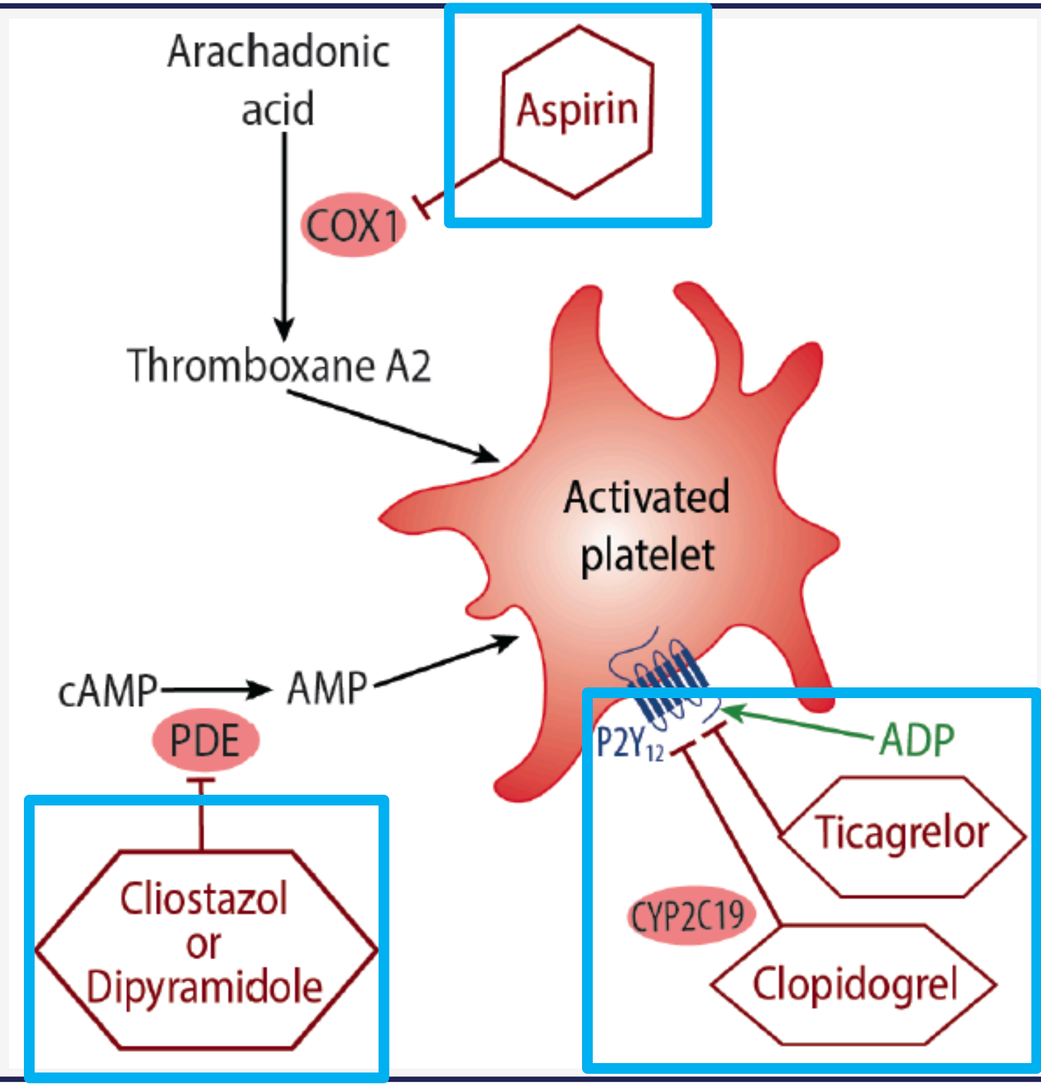
- I have no relevant financial relationships to disclose.
- My talk will include off -label discussion.

Objectives

1. Discuss mechanisms of action, dosages, and other characteristics of antiplatelet medications used for secondary stroke prevention.

2. Assess the place in therapy of antiplatelet medications and dual antiplatelet therapy (DAPT).

Mechanisms of Action



1. Indraswari F, et al. *Practical Neurology (US)*. 2022;21(1):34-39.

COX1 = cyclooxygenase -1; AMP = adenosine monophosphate; cAMP = cyclic AMP; PDE = phosphodiesterase; ADP = adenosine diphosphate; CYP2C19 = cytochrome P450 2C19

Aspirin

Dosing

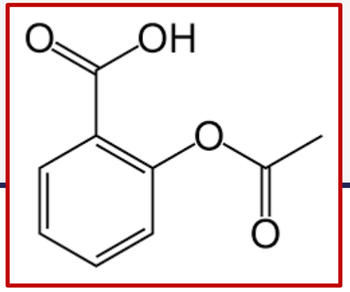
- Loading dose: 160 -325 mg by mouth once
- Maintenance dose: 50 -325 mg by mouth once daily

Adverse Effects

- Bleeding
- Gastrointestinal effects (e.g., ulcers, dyspepsia, peptic ulcer disease, hemorrhage)
- Hypersensitivity reactions

Other Considerations

- Take with food or a full glass of water
- Avoid use in severe hepatic impairment



2. Aspirin [prescribing information]. November 2023.

Dipyridamole + Aspirin

Dosing

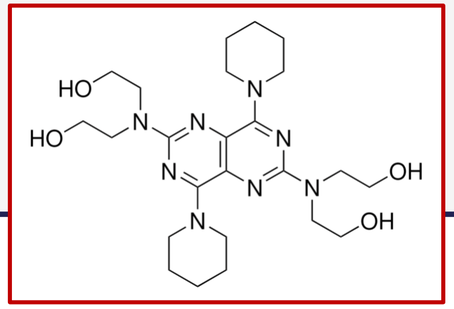
- No loading dose
- Aspirin 25 mg/dipyridamole ER 200 mg by mouth twice daily

Adverse Effects

- Most common (>1%): headache, abdominal pain, dyspepsia, nausea, diarrhea, vomiting, hemorrhage

Other Considerations

- Use with caution in patients with hypotension, unstable angina, and/or recent myocardial infarction
- Avoid use if GFR < 10 mL/minute or severe hepatic impairment



3. Aspirin/dipyridamole ER [prescribing information]. December 2023.

ER = extended release; GFR = glomerular filtration rate

Clopidogrel

Dosing

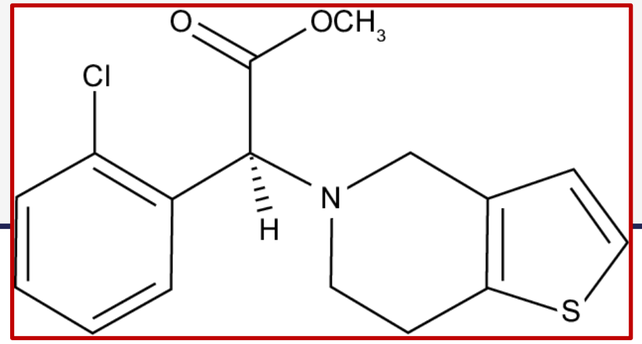
- Loading dose: 300 -600 mg by mouth once
- Maintenance dose: 75 mg by mouth once daily

Adverse Effects

- Most common (1 -10%): major or minor hemorrhage
- Thrombotic thrombocytopenic purpura
- Hypersensitivity reactions

Other Considerations

- Avoid or minimize consumption of grapefruit juice



4. Clopidogrel [prescribing information]. May 2024.

Ticagrelor

Dosing

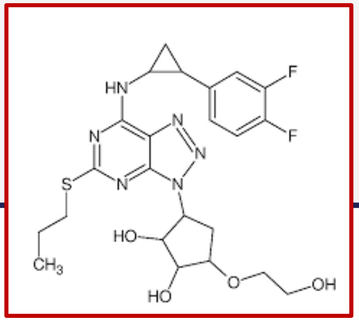
- Loading dose: 180 mg once by mouth once
- Maintenance dose: 90 mg by mouth twice daily

Adverse Effects

- Most common (>1%): dyspnea, gout, ECG abnormalities (e.g., ventricular pause and bradyarrhythmias), nausea, hemorrhage, dizziness, increased serum creatinine
- Thrombotic thrombocytopenic purpura

Other Considerations

- Contraindicated if history of intracranial hemorrhage **(boxed warning)**
- Avoid use in severe hepatic impairment



5. Ticagrelor [prescribing information]. July 2020.

Cilostazol

Dosing (off -label)

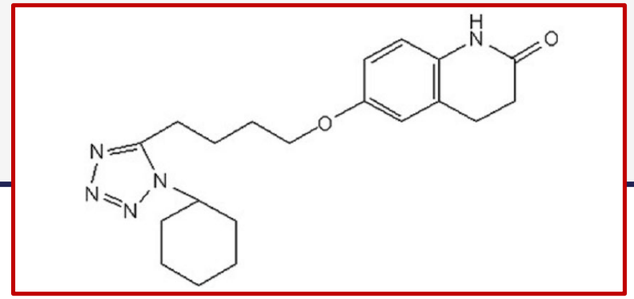
- No loading dose
- 100 mg by mouth twice daily on an empty stomach

Adverse Effects

- Most common (>10%): headache, diarrhea, abnormal stools, infection, rhinitis
- Cardiovascular effects (e.g., tachycardia, palpitations, tachyarrhythmia, hypotension)
- Hematologic effects (e.g., thrombocytopenia, leukopenia)

Other Considerations

- Only FDA-approved indication is intermittent claudication
- Contraindicated in heart failure (boxed warning)
- Dose adjustment needed if regular consumption of grapefruit juice



6. Cilostazol [prescribing information]. April 2024.

FDA = Food and Drug Administration

Drug-Drug Interactions

Antiplatelet	Metabolism/Transport Effects	Select Drug Interactions
Aspirin +/ - dipyridamole [2,3]	• Aspirin: minor CYP2C9 substrate • Dipyridamole: none known	• Avoid use of other NSAIDs if possible
Clopidogrel [4]	• Major CYP2C19 substrate • Minor CYP3A4 substrate • Inhibitor of BCRP/ABCG2, CYP2B6 (weak), CYP2C8 (moderate)	• Avoid use with omeprazole and esomeprazole • Avoid use with strong CYP2C19 inhibitors and inducers if possible
Ticagrelor [5]	• Major CYP3A4 substrate • Inhibitor of BCRP/ABCG2	• Avoid use with strong CYP3A4 inducers and inhibitors • Limit lovastatin and simvastatin to 40 mg/day, aspirin to 100 mg/day
Cilostazol [6]	• Major CYP2C19 and CYP3A4 substrate • Minor CYP1A2 and CYP2D6 substrate • Weak inhibitor of CYP3A4	• Decrease dose to 50 mg twice daily when used with omeprazole, moderate CYP2C19 inhibitors, and moderate or strong CYP3A4 inhibitors

BCRP/ABCG2 = breast cancer resistance protein/ATP -binding cassette G2 transporter

2. Aspirin [prescribing information]. November 2023.
3. Aspirin/dipyridamole ER [prescribing information]. December 2023.
4. Clopidogrel [prescribing information]. May 2024.
5. Ticagrelor [prescribing information]. July 2020.
6. Cilostazol [prescribing information]. April 2024.

Guideline Recommendations[7]: Short-Term DAPT

Aspirin + Clopidogrel

- For 21-90 days after recent (≤ 7 days, ideally < 12-24 hours) minor noncardioembolic ischemic stroke (NIHSS score ≤ 3) or high-risk TIA ($ABCD^2$ score ≥ 4)
- For up to 90 days after recent (< 30 days) stroke or TIA caused by 70-99% stenosis of major intracranial artery

Aspirin + Ticagrelor

- May be considered for up to 30 days after recent (< 24 hours) minor-to-moderate stroke (NIHSS score ≤ 5), high-risk TIA ($ABCD^2$ score ≥ 6), or symptomatic ≥ 30% stenosis of intracranial or extracranial artery that could account for the event
- Might be considered for 30 days after recent (< 24 hours) minor stroke or high-risk TIA and concomitant ipsilateral >30% stenosis of a major intracranial artery

7. Kleindorfer DO, et al. *Stroke*. 2021;52(7):e364 -e467.

DAPT = dual antiplatelet therapy; NIHSS = National Institutes of Health Stroke Scale; TIA = transient ischemic attack

DAPT Clinical Trials

Trial	Study Population	Interventions	Outcomes
CHANCE[8] N = 5,170	• Minor ischemic stroke (NIHSS score ≤ 3) or high-risk TIA (ABCD^2 score ≥ 4) • Within 24 hours of symptom onset	90-day regimen of either: • Clopidogrel (300 mg x1 , then 75 mg daily) + aspirin (for 21 days) • Placebo + aspirin *Aspirin dosing: 75-300 mg x1, then 75 mg daily*	• Stroke: 8.2% vs. 11.7% (HR 0.68; 95% CI 0.57-0.81; P < 0.001) • Moderate or severe hemorrhage: 0.3% vs. 0.3% (P = 0.73)
POINT[9] N = 4,881	• Minor ischemic stroke (NIHSS score ≤ 3) or high-risk TIA (ABCD^2 score ≥ 4) • Within 12 hours of symptom onset	90-day regimen of either: • Clopidogrel (600 mg x1 , then 75 mg daily) + aspirin • Placebo + aspirin *Aspirin dosing: 50-325 mg daily*	• Major ischemic events: 5.0% vs. 6.5% (HR 0.75; 95% CI 0.59 - 0.95; P = 0.02) • Major hemorrhage: 0.9% vs. 0.4% (HR 2.32; 95% CI 1.10-4.87; P = 0.02)

HR = hazard ratio; CI = confidence interval

8. Wang Y, et al. *N Engl J Med*. 2013;369(1):11-9.
9. Johnston SC, et al. *N Engl J Med*. 2018;379(3):215-225.

DAPT Clinical Trials (cont.)

Trial	Study Population	Interventions	Outcomes
SAMMPRIS[10] N = 451	• Stroke or TIA caused by 70-99% stenosis of major intracranial artery • Within 30 days of symptom onset	• Aspirin (325 mg daily) + clopidogrel (75 mg daily for 90 days) + management of risk factors alone vs. addition of percutaneous transluminal angioplasty and stenting	• Stroke or death within 1-year: 12.2% vs. 20.0% • In a previous trial, recurrent stroke risk at 1-year with aspirin alone was ~23%[11]
THALES[12] N = 11,016	• Mild-to-moderate acute noncardioembolic ischemic stroke (NIHSS score ≤ 5) or high-risk TIA (ABCD^2 score ≥ 6 or symptomatic ≥ 50% stenosis of intracranial or extracranial artery) • Within 24 hours of symptom onset	30-day regimen of either: • Ticagrelor (180 mg x1, then 90 mg twice daily) + aspirin • Placebo + aspirin *Aspirin dosing: 300-325 mg x1, then 75-100 mg daily*	• Composite of stroke or death: 5.5% vs. 6.6% (HR 0.83; 95% CI 0.71-0.96; P = 0.02) • Severe bleeding: 0.5% vs. 0.1% (HR 3.99; 95% CI 1.74-9.14; P = 0.001)

10. Chimowitz MI, et al. *N Engl J Med*. 2011;365(11):993-1003.
11. Kasner SE, et al. *Circulation*. 2006;113(4):555-63.
12. Johnston SC, et al. *N Engl J Med*. 2020;383(3):207-217.

Recent DAPT Clinical Trials

- Current guideline recommendation based on SAMMPRIS trial:
  - Aspirin + clopidogrel for up to 90 days after recent (< 30 days) stroke or TIA caused by 70 -99% stenosis of major intracranial artery [7]

Trial	Study Population	Interventions	Outcomes
INSPIRES[13] N = 6,100	• Mild ischemic stroke (NIHSS score ≤ 5) or high-risk TIA ($ABCD^2$ score ≥ 4) • Caused by ≥ 50% stenosis of major intracranial or extracranial artery **OR** acute new multiple infarctions of presumed large -artery atherosclerosis origin • Within 72 hours of symptom onset	90-day regimen of either: • Clopidogrel (300 mg x1, then 75 mg daily) + aspirin (for 21 days) • Placebo + aspirin *Aspirin dosing: 100 -300 mg x1, then 100 mg daily*	• Stroke: 7.3% vs. 9.2% (HR 0.79; 95% CI 0.66 -0.94; P = 0.008) • Moderate -to-severe bleeding: 0.9% vs. 0.4% (HR 2.08; 95% CI 1.07 -4.04; P = 0.03)

7. Kleindorfer DO, et al. *Stroke*. 2021;52(7):e364 -e467.
13. Gao Y, et al. *N Engl J Med*. 2023 ;389(26):2413 -2424.

Recent DAPT Clinical Trials (cont.)

- Clopidogrel resistance is caused by multiple factors, including: [14]
  - Chronic kidney disease
  - Drug interactions
  - Genetic factors (e.g., having at least one CYP2C19 loss-of-function allele)
- Available tests for resistance: [15]
  - Genetic tests for CYP2C19 polymorphisms
  - Platelet function tests
    - High on-treatment platelet reactivity has been associated with multiple adverse outcomes, including recurrent vascular events [16,17]

Trial	Study Population	Interventions	Outcomes
CHANCE-2[18] N = 11,255	• Mild ischemic stroke (NIHSS score $\leq$ 3) or high-risk TIA (ABCD^2 score $\geq$ 4) • Carrier of a CYP2C19 loss-of-function allele • Within 24 hours of symptom onset	90-day regimen of either: • Ticagrelor + aspirin (for 21 days) • Clopidogrel + aspirin (for 21 days)	• Stroke: 6.0% vs. 7.6% (HR 0.77; 95% CI 0.64 - 0.94; P = 0.008) • Severe or moderate bleeding: 0.3% vs. 0.3% (HR 0.82; 95% CI 0.34 -1.98; P = 0.66)

14. Wiśniewski A. *Medicina (Kaunas).* 2021;57(1):59.
15. Krishnan K, et al. *Stroke Vasc Interv Neurol*. 2023;3:e000576.
16. Zhou K, et al. *Acta Neurol Scand* . 2022;146(3):205-224.
17. Lim ST, et al. *J Neurol*. 2020;267(10):3021-3037.
18. Wang Y, et al. *N Engl J Med*. 2021;385(27):2520-2530.

Guideline Recommendations[7]: Long-Term Antiplatelet Therapy

Noncardioembolic Ischemic Stroke or TIA

- Aspirin 50-325 mg daily
- Clopidogrel 75 mg daily
- Aspirin 25mg/Dipyridamole ER 200 mg twice daily

Intracranial Large Artery Atherosclerosis

- Aspirin 325 mg daily (if stroke or TIA caused by 50-99% stenosis of major intracranial artery)
- Cilostazol 100 mg twice daily + aspirin/clopidogrel (might be considered after stroke or TIA caused by 50-99% stenosis of a major intracranial artery)

7. Kleindorfer DO, et al. *Stroke*. 2021;52(7):e364 -e467.

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References

1. Indraswari F, Dai X, Shu L, et al. Antiplatelet therapies after ischemic stroke. *Practical Neurology (US)*. 2022;21(1):34-39.
2. Aspirin [prescribing information]. Morristown, NJ; Bayer HealthCare LLC; November 2023.
3. Aspirin/dipyridamole ER [prescribing information]. Memphis, TN: NorthStar Rx LLC; December 2023.
4. Clopidogrel [prescribing information]. Parsippany, NJ: Ascend Laboratories LLC; May 2024.
5. Ticagrelor [prescribing information]. Bridgewater, NJ: Amneal Pharmaceuticals NY LLC; July 2020.
6. Cilostazol [prescribing information]. Columbus, OH: Slate Run Pharmaceuticals LLC; April 2024.
7. Kleindorfer DO, Towfighi A, Chaturvedi S, et al. 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. *Stroke*. 2021;52(7):e364-e467.
8. 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.
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12. Johnston SC, Amarenco P, Denison H, et al; THALES Investigators. Ticagrelor and aspirin or aspirin alone in acute ischemic stroke or TIA. *N Engl J Med*. 2020;383(3):207-217.
13. Gao Y, Chen W, Pan Y, et al; INSPIRES Investigators. Dual antiplatelet treatment up to 72 hours after ischemic stroke. *N Engl J Med*. 2023;389(26):2413-2424.
14. Wiśniewski A. Multifactorial background for a low biological response to antiplatelet agents used in stroke prevention. *Medicina (Kaunas)*. 2021;57(1):59.
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