Aspirin

Aspirin

- Mechanism of action
- Aspirin in Primary Prevention
  - *ASPREE*
  - ASCEND
  - ARRIVE
- Bleeding risks
- Aspirin in Secondary Prevention

Aspirin Mechanism

- Willow bark contains salicylates and was used for analgesia > 3500 years ago by the Sumerians and Egyptians.
- **Mechanism of action:**
  - **Irreversibly inhibits Cyclooxygenase (COX-1 and COX-2)**
  - COX-1 leads to production of prostaglandins
    - protect gastric mucosa
    - maintain renal blood flow
    - regulate platelet activation and aggregation.
  - COX-2 expression is induced by inflammation
    - promotes the inflammatory response.
  - **Blocking COX-1 and/or COX-2 leads to reduced production of prostaglandins and thromboxane**
    - Reduced inflammation
    - Inhibition of platelet aggregation

Aspirin | Circulation (ahajournals.org)

Aspirin Mechanism

- Plasma half-life of 20 minutes
- Platelets have no nucleus and limited mRNA/protein synthesis
  - COX-1 inhibition in platelets is irreversible and lasts until the platelet is destroyed and replaced.
  - Platelet life ~10 days
- May protect LDL from oxidation
- Improves endothelial dysfunction in atherosclerotic vessels
- Antioxidant effects
- probably other effects that lead to reduced inflammatory response

Aspirin | Circulation (ahajournals.org)

Aspirin Mechanism

- Rapidly absorbed in upper GI tract
  - inhibits platelet function within 60 minutes
  - **Enteric coating significantly delays absorption**
    - **BUT, does not seem to reduce GI Bleeding risk**
    - Risk of aspirin-associated major upper-gastrointestinal bleeding with enteric-coated or buffered product - PubMed (nih.gov)

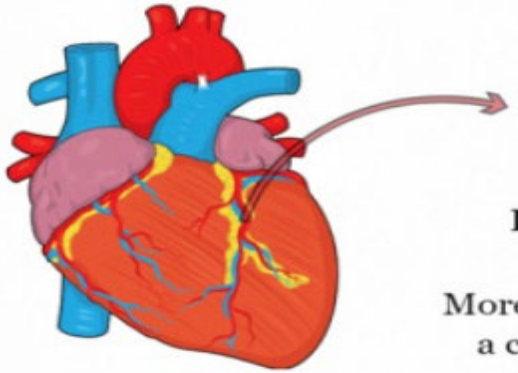
- Single 100mg dose stops Thromboxane synthesis
- Effect of daily dosing is cumulative.
- Higher doses not proven to be more effective for antiplatelet effects and increase GI side effects.

Aspirin | Circulation (ahajournals.org)

Aspirin: Its role in coronary heart disease

Aspirin reduces platelet aggregation and thrombus formation by COX-1 inhibition and impeding thromboxane A2 production.

Higher doses lead to COX-2 inhibition and subsequent decreased prostacyclin and prostaglandin E production, which results in analgesic and antipyretic effects.



Primary prevention

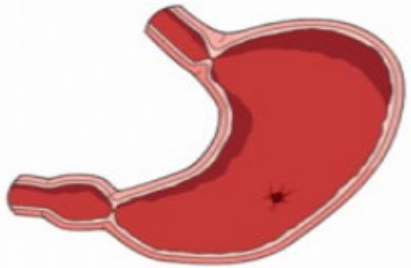
More recent trials fail to show a consistent benefit in the context of a changing population with greater control of other risk factors.

Secondary prevention

Aspirin demonstrates a clear benefit and is recommended for life after a CHD diagnosis; however, further studies are needed to clarify whether aspirin vs a P2Y12 inhibitor is the better monotherapy after 12 months of DAPT.

...and its gastrointestinal bleeding risks

Aspirin increases the risk of GI bleeding by topical mucosal injury and through significant reductions in prostaglandin levels through COX inhibition.



Enteric coating, lifestyle modifications (eg, reducing alcohol intake), different aspirin formulations and the use of bleeding risk scores may help reduce this risk.

Aspirin in the Modern Era of Cardiovascular Disease Prevention - PMC (nih.gov)

Methodist Debakey Cardiovasc J. 2021; 17(4): 36–47.
Published online 2021 Sep 24. doi: 10.14797/mdcvj.293

The role of aspirin in primary and secondary prevention. COX: cyclooxygenase isoenzyme; CHD: coronary heart disease; P2Y12: a chemoreceptor for adenosine diphosphate DAPT: dual antiplatelet therapy; GI: gastrointestinal.

Aspirin for CVD Primary Prevention

ASPREE Trial 2018
ASPirin in Reducing Events in the Elderly

- Aspirin 100mg qd vs Placebo. n = 19,114; Median of 4.7 years of follow-up
- Randomized, double-blind, placebo-controlled trial of daily low-dose aspirin (100 mg) in older adults in US and Australia.
- **Healthy individuals >70 y/o (or >65 y/o for blacks and Hispanics)**; avg age 74; female 56%; Diabetic 11%
- Public Funding: United States and Australian governments and is led by the Berman Centre for Outcomes and Clinical Research in the U.S. and Monash University in Australia.
- Exclusion criteria: cardiovascular or cerebrovascular disease, dementia, high bleeding risk
- Primary Outcome: all-cause death, dementia, or physical disability
- Secondary outcome: Hemorrhage, stroke, MI, hospitalization for heart failure, fatal CVD, cancer

ASPREE Results

Aspirin did not prolong disability-free survival

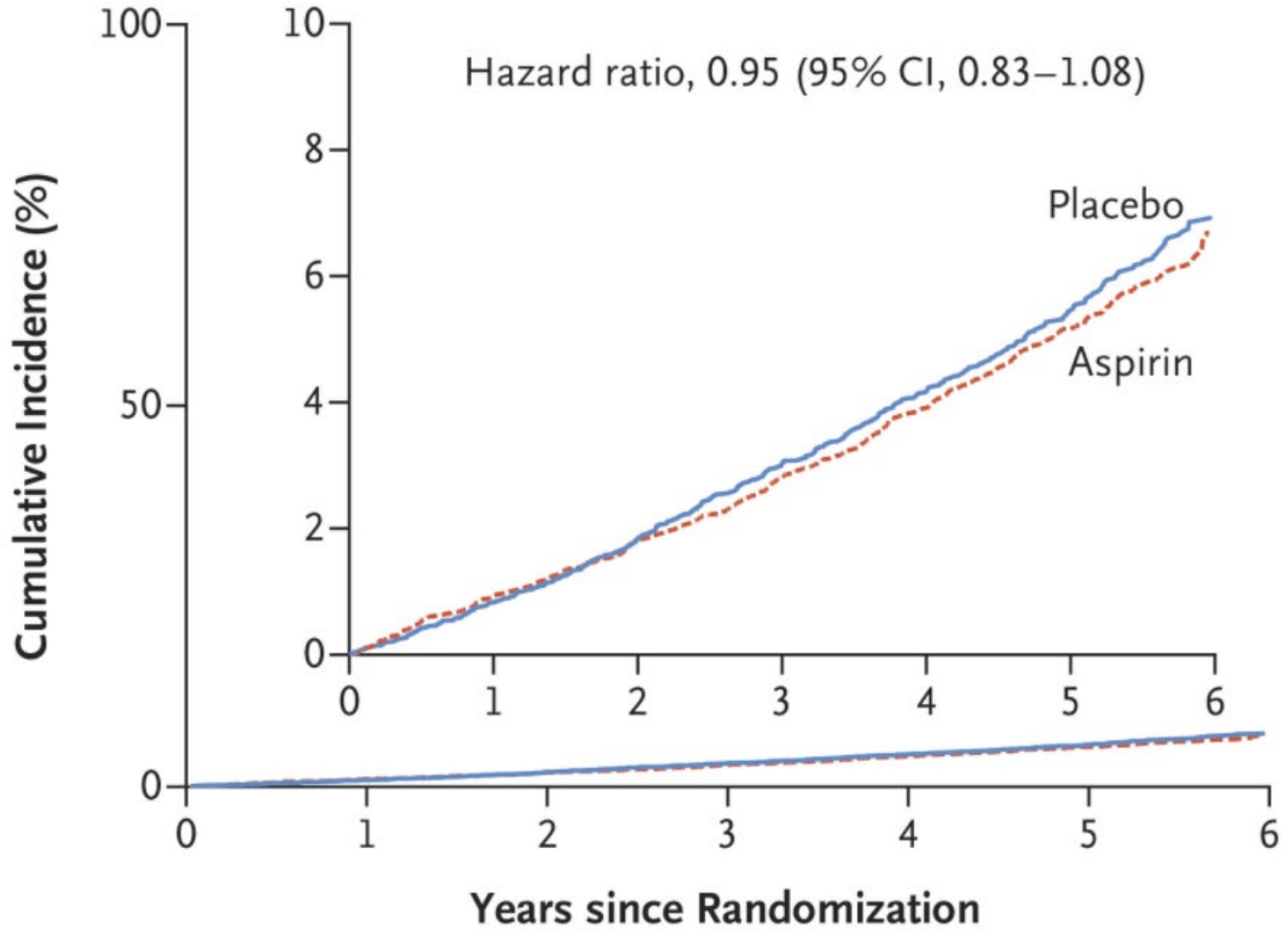
Primary outcomes (Events per 1000 person-years)

- All-cause death, dementia, or physical disability
- **Aspirin did not prolong disability-free survival**
- 12.7 aspirin vs 11.1 placebo
- HR 1.14; 95% CI 1.01 - 1.29
- Cancer contribution to death was higher in the aspirin group
  - HR 1.31, 95% CI 1.10-1.56

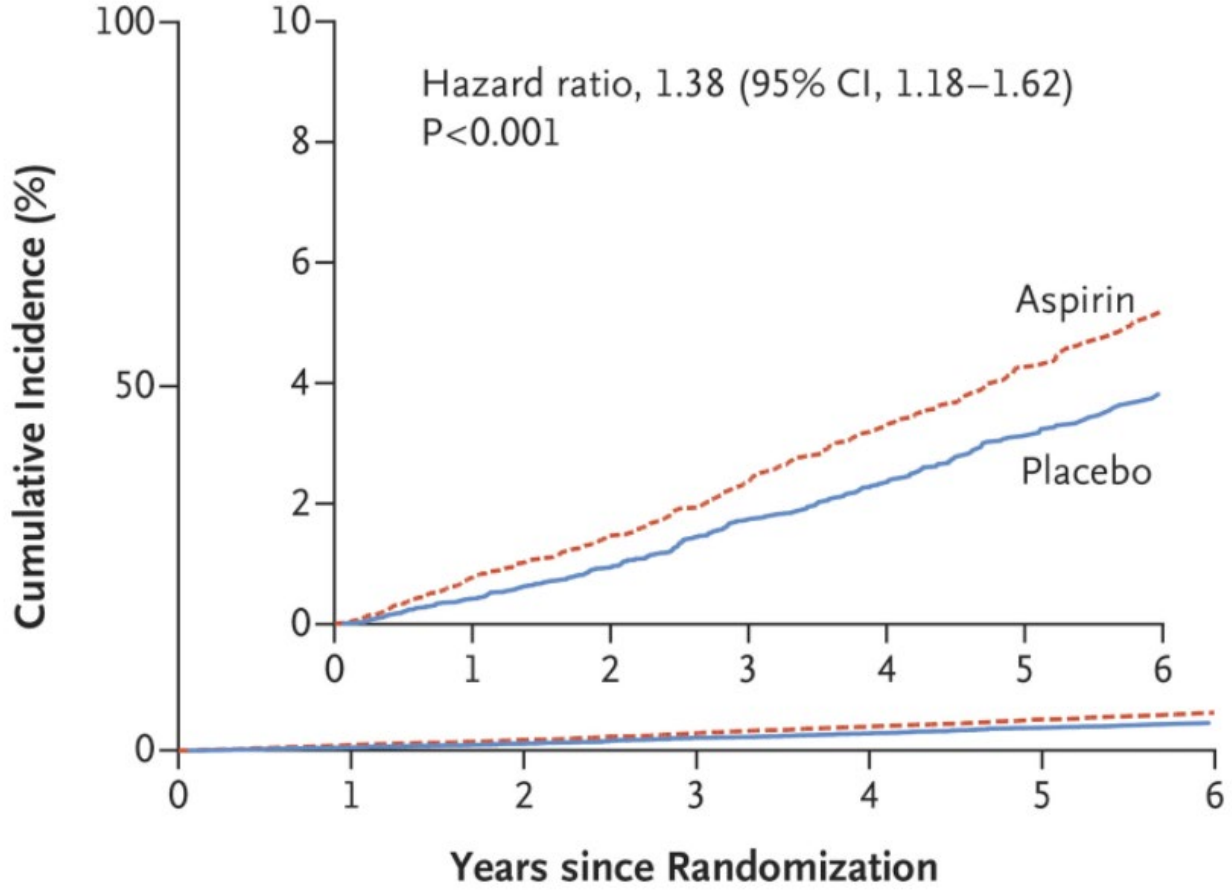
Secondary outcomes (Events per 1000 person-years)

- CVD event: 10.7 aspirin vs 11.3 placebo (p = 0.79)
- Major CV event: 7.8 aspirin vs 8.8 placebo (p=0.89)
- **Major hemorrhage: 8.6 aspirin vs 6.2 placebo (p <0.001)**
- **Intracranial bleeding: 2.5 aspirin vs 1.7 placebo (p <0.05)**
- **Upper GI bleed: 2.1 aspirin vs 1.1 placebo (p <0.05)**

ASPREE
Cumulative Incidence of Cardiovascular Disease



ASPREE
Cumulative Incidence of Major Hemorrhage



ASPREE Trial Results

- Effect of Aspirin on All-Cause Mortality in the Healthy Elderly - PubMed (nih.gov) N Engl J Med. 2018;379(16):1519.
  - **Higher all-cause mortality was observed among apparently healthy older adults who received daily aspirin** than among those who received placebo and was attributed primarily to cancer-related death.
- Effect of Aspirin on Disability-free Survival in the Healthy Elderly - PubMed (nih.gov) N Engl J Med. 2018;379(16):1499.
  - **Aspirin use in healthy elderly persons did not prolong disability-free survival over a period of 5 years but led to a higher rate of major hemorrhage than placebo.**
- Effect of Aspirin on Cardiovascular Events and Bleeding in the Healthy Elderly | NEJM. N Engl J Med. 2018;379(16):1509.
  - The use of low-dose aspirin as a primary prevention strategy in older adults **resulted in a significantly higher risk of major hemorrhage and did not result in a significantly lower risk of cardiovascular disease** than placebo.
  - Higher mortality in aspirin group.

Interpretation of ASPREE

Among HEALTHY elderly patients low-dose aspirin therapy for primary prevention was not beneficial at 4.7 years follow up.

- No improvement in disability-free survival, CVD events, cancer
- Increased risk of major bleeding and mortality

BUT…the subjects were **healthy elderly patients**

- Exclusion criteria: cardiovascular or cerebrovascular disease, dementia, high bleeding risk
- Closer to our population than most studies but not quite there yet.

Summary of Study -- Aspirin in Reducing Events in the Elderly - American College of Cardiology (acc.org)

Safety of Ceasing Aspirin Used Without a Clinical Indication After Age 70 Years: A Subgroup Analysis of the ASPREE Randomized Trial

- ASPREE was interpreted by some to be relevant only to ***initiation*** of Aspirin and not ***discontinuation*** of Aspirin
- Study tried to use ASPREE data to answer if aspirin cessation among consistent users had an effect on survival
- Not enough statistical power – Inconclusive
- Perhaps the ASPREE-XT will improve statistical power

Safety of Ceasing Aspirin Used Without a Clinical Indication After Age 70 Years: A Subgroup Analysis of the ASPREE Randomized Trial | Annals of Internal Medicine (acpjournals.org)

ASPREE Project Continues

- Big project with lots of sub-studies
- https://aspree.org/usa
- ASPREE-XT -- continuation of ASPREE trial beyond 4.7 years
- ASPREE Cancer Endpoints Study (ACES)
- ASPREE Cancer Treatment Study (ACTS)
- ASPREE-D (Depression)
- ASPREE-EWAS (Epigenetics)
- ASPREE-G (Genomics)
- ASPREE Longitudinal Study of Older Persons (ALSOP)
- ASPREE-XT Microbiome

ASCEND Trial 2018

Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus - NEJM

- RCT of Aspirin 100mg qd vs placebo; N 15,480; type 2 DM w/out evidence of CVD; follow-up of 7.4 years
- Primary outcome: first serious vascular event (MI, CVA/TIA, vascular related death, excluding intracranial hemorrhage)

- **Vascular events significantly lowered**
  - Aspirin 8.5% vs. Placebo 9.6% (rate ratio 0.88; 95% CI, 0.79 - 0.97; P=0.01)

- **Major bleeding events were significantly increased**
  - Aspirin 314 participants (4.1%) vs Placebo 245 (3.2%) (rate ratio 1.29; 95% CI, 1.09 - 1.52; P=0.003),
  - Mostly GI bleeding and other extracranial bleeding.

- No significant difference in the incidence of GI tract cancer

- **Aspirin use prevented serious vascular events in persons who had diabetes and no evident cardiovascular disease but caused major bleeding events.** The absolute benefits were largely counterbalanced by the bleeding hazard.

ARRIVE Trial 2018
Aspirin to Reduce Risk of Initial Vascular Events

Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE)

- Aspirin 100mg qd vs placebo; n = 12,546; Median follow up 5 yrs
- Primary care setting, double-blinded, placebo-controlled, multicenter study (7 countries); nondiabetic patients with a moderate risk (ASCVD 10–20% 10-year risk) of CAD
- Men >50 y/o; Women >60 y/o; avg age 63.9
- Primary outcome: Cardiovascular death, MI, unstable angina, CVA/TIA
- Exclusion criteria: High risk of bleeding, diabetes

- **Aspirin did not lower the risk of major CV events**
  - Aspirin 4.3% vs placebo 4.5% (p=0.60)

- **Significant number of GI bleeds**
  - aspirin 61 (0.97%) vs Placebo 29 (0.46%) (p=0·0007)
  - Even though high GI bleed risk was an exclusion criteria.

Summary - Aspirin to Reduce Risk of Initial Vascular Events - American College of Cardiology (acc.org)

Do we see a trend?

- Probably not much cardiovascular benefit

- High risk of bleeding

2019 ACC/AHA Guideline for Primary Prevention of CVD

Recommendations for Aspirin Use

Referenced studies that support recommendations are summarized in Online Data Supplements 17 and 18.

COR	LOE	Recommendations
IIb	A	1. Low-dose aspirin (75-100 mg orally daily) might be considered for the primary prevention of ASCVD among select adults 40 to 70 years of age who are at higher ASCVD risk but not at increased bleeding risk.[S4.6-1–S4.6-8]
III: Harm	B-R	2. Low-dose aspirin (75-100 mg orally daily) should not be administered on a routine basis for the primary prevention of ASCVD among adults >70 years of age.[S4.6-9]
III: Harm	C-LD	3. Low-dose aspirin (75-100 mg orally daily) should not be administered for the primary prevention of ASCVD among adults of any age who are at increased risk of bleeding.[S4.6-10]

IIb → Benefit equal to or greater than risk
A → High quality evidence

III: Harm → Risk > Benefit
B-R → Moderate quality evidence; 1 or more RCTs

III: Harm → Risk > Benefit
C-LD → Limited Data. Observational studies. Limitations in design.

2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines | Circulation (ahajournals.org)

USPSTF Update Pending

[Draft Recommendation: Aspirin Use to Prevent Cardiovascular Disease: Preventive Medication | United States Preventive Services Taskforce (uspreventiveservicestaskforce.org)]

USPSTF changing recommend from “insufficient evidence” to recommending against starting aspirin for primary prevention in > 60 y/o

Draft Recommendation Statement

Aspirin Use to Prevent Cardiovascular Disease: Preventive Medication

October 12, 2021

Recommendations made by the USPSTF are independent of the U.S. government. They should not be construed as an official position of the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

This topic is being updated. Please use the link(s) below to see the latest documents available.
Update in Progress for Aspirin Use to Prevent Cardiovascular Disease: Preventive Medication

Recommendation Summary

Population	Recommendation	Grade
Adults ages 40 to 59 years with a 10% or greater 10-year cardiovascular disease (CVD) risk	The decision to initiate low-dose aspirin use for the primary prevention of CVD in adults ages 40 to 59 years who have a 10% or greater 10-year CVD risk should be an individual one. Evidence indicates that the net benefit of aspirin use in this group is small. Persons who are not at increased risk for bleeding and are willing to take low-dose aspirin daily are more likely to benefit.	C
Adults age 60 years or older	The USPSTF recommends against initiating low-dose aspirin use for the primary prevention of CVD in adults age 60 years or older.	D

Risk of Bleeding with Aspirin

- **Significant number of bleeding events in ASPREE, ASCEND, and ARRIVE**
- Mostly GI bleeding but some intracranial
- Mortality from non-traumatic intracranial bleeding ~ 40%
- **Lower dose, lower risk of bleeding**
  - "…limited justification to use aspirin doses >100mg daily for primary prevention." 2019 ACC/AHA Guideline of PP of CVD
  - Analysis of risk of bleeding complications after different doses of aspirin in 192,036 patients enrolled in 31 randomized controlled trials - PubMed (nih.gov)

Risk of Bleeding with Aspirin

- Bleeding Risks With Aspirin Use for Primary Prevention in Adults: A Systematic Review for the U.S. Preventive Services Task Force - PubMed (nih.gov) 2016
  - 58% increased risk in GI bleeding (OR 1.58, 95% CI 1.29 -1.95])
  - 27% increase in hemorrhagic stroke risk (OR 1.27, CI 0.96 - 1.68])

- Frequency of Intracranial Hemorrhage With Low-Dose Aspirin in Individuals Without Symptomatic Cardiovascular Disease: A Systematic Review and Meta-analysis - PubMed (nih.gov)
  - 13 RCTs including ASCEND, ARRIVE, ASPREE
  - Assess risk of Intracranial hemorrhage in individuals without symptomatic CVD
  - Low- dose aspirin vs placebo
  - Increased risk of intracranial bleeding (RR 1.37, 95% CI 1.13-1.66)

Risk of Bleeding with Aspirin

- Bleeding risk of aspirin is significant
- This same risk probably applies to **secondary prevention** as well.
- What factors trump the bleeding risk for primary prevention? Secondary prevention?
  - Family hx
  - Poorly controlled HTN/HLD
  - Elevated Coronary Ca++ score
  - ASCVD score >10%
- Does a PPI or H2 blocker reduce GI bleeding risk?
  - Age-specific risks, severity, time course, and outcome of bleeding on long-term antiplatelet treatment after vascular events: a population-based cohort study - PMC (nih.gov)

Aspirin for Secondary Prevention of CVD

- What about the data supporting aspirin for secondary prevention
  - Acute MI, unstable angina
  - Acute ischemic stroke, post stroke
  - CAD, post CABG, post MI, PCI/stents
  - PAD, Carotid artery disease
- **Data showing efficacy of aspirin in the acute setting is strong**
  - Anti-Thrombotic Trialists' Collaboration meta-analysis (1970s, 1980s)
- **Data showing efficacy of aspirin for lifelong secondary prevention is lacking**
  - Follow periods of 4 years in most studies.
- **Studies using various combinations of P2Y12 inhibitors, aspirin, and anticoagulants are underway.**

Lifelong Aspirin for All in the Secondary Prevention of Chronic Coronary Syndrome | Circulation (ahajournals.org)

Is it time for a study looking at discontinuation of aspirin for secondary prevention in the elderly?

A Alternative strategies. Recent trials of early aspirin discontinuation from post PCI DAPT and among CCS patients on OAC

B Bleeding. Bleeding risk increasingly recognized, particularly among the elderly; challenging lifelong aspirin therapy

C Contemporary therapy. Recent null primary prevention trials highlight a potential reduction in efficacy of aspirin among patients treated to modern RF targets

Aspirin Topics for the future

Role of aspirin in

- PVD
- Primary/Secondary Prevention of Stroke
- Atrial Fibrillation
  - Comparison of aspirin and DOACs
- DVT prophylaxis
  - Post hip fracture
  - Comparison of aspirin and DOACs

Thank you for listening

David Shepherd

Aspirin Part II

- Aspirin for ischemic stroke prevention
  - Primary prevention
  - Treatment of acute stroke
  - Secondary prevention
  - Stopping aspirin for stroke prevention
- Aspirin for prevention of cardioembolic stroke in Afib
  - Does aspirin prevent cardioembolic stroke?
  - Bleeding risk
    - Aspirin vs warfarin
    - Warfarin vs DOACs
    - DOAC vs aspirin
- Aspirin in PAD/PVD
  - Current recs
  - Newer data
- Aspirin Scorecard

Aspirin for Stroke Prevention

Aspirin: Primary Prevention of Stroke

- ASPREE and ARRIVE
  - **Aspirin did not lower CVD events**
  - **Did not prolong disability free survival**
  - **Raised risk of major hemorrhage**
  - **Raised risk of mortality (primarily related to cancer)**

- USPSTF
  - Against aspirin for primary prevention in those > 60
  - Small benefit in those 40-59 y/o with 10% 10-year CVD risk

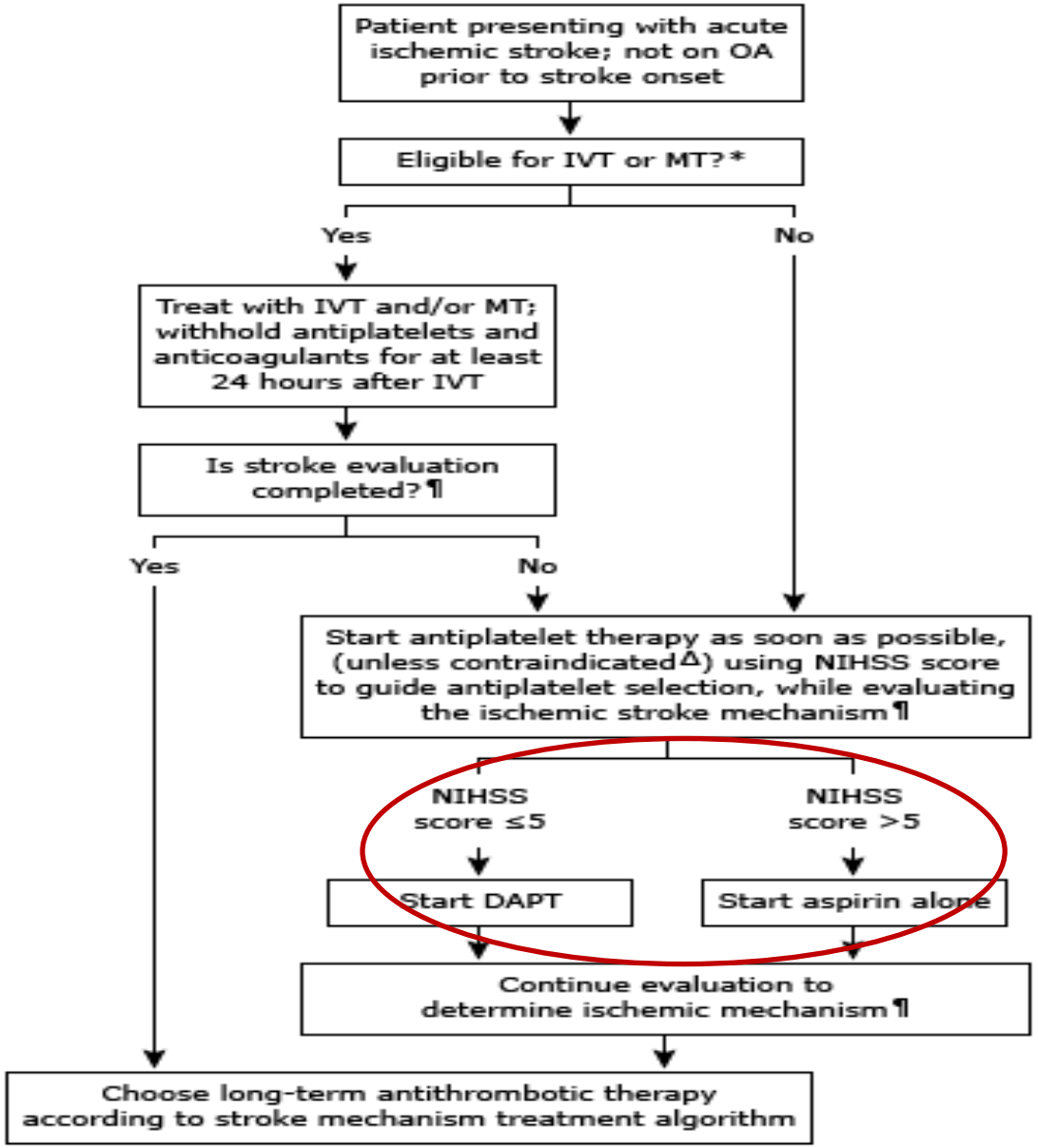
Aspirin Use to Prevent Cardiovascular Disease: US Preventive Services Task Force Recommendation Statement | Cardiology | JAMA | JAMA Network

Aspirin Tx of Acute Ischemic Stroke

- Risk of recurrence is high in the hours and days after stroke
- Recurrence in this time is associated with high fatality
- **Aspirin within 48 hours is beneficial**
  - Fewer recurrent ischemic strokes
  - More hemorrhagic transformation?
- International Stroke Trial 1997
  - 10 deaths or recurrent strokes avoided per 1000
- Chinese Acute Stroke Trial
  - 14% reduction in mortality

Antiplatelet Therapy After Noncardioembolic Stroke | Stroke (ahajournals.org)
Cumulative meta-analysis of aspirin efficacy after cerebral ischaemia of arterial origin - PMC (nih.gov)

Immediate antithrombotic treatment of acute ischemic stroke



NIHSS

Score [3]	Stroke severity
0	No stroke symptoms
1–4	Minor stroke
5–15	Moderate stroke
16–20	Moderate to severe stroke
21–42	Severe stroke

This algorithm is intended to provide basic guidance regarding the immediated use of antithrombotic therapy for patients with an acute ischemic stroke. For further details, including scoring of the NIHSS and suggested dosing regimens of antithrombotic agents, refer to the relevant UpToDate topic reviews.

OA: oral anticoagulants; IVT: intravenous thrombolysis; MT: mechanical thrombectomy; NIHSS: National Institutes of Health Stroke Scale; DAPT: dual antiplatelet therapy (eg, aspirin and clopidogrel, or aspirin and ticagrelor).

* Refer to text and associated algorithm for details.

¶ Brain and large vessel imaging, cardiac evaluation, and (for select patients) other laboratory tests.

Δ For severe systemic or symptomatic intracranial bleeding, withhold all anticoagulant and antiplatelet therapy for one to two weeks or until the patient is stable.

Aspirin: Secondary Prevention

Effects of aspirin on risk and severity of early recurrent stroke after transient ischaemic attack and ischaemic stroke: time-course analysis of randomised trials - The Lancet 2016

- Meta-analysis, 12 trials, randomized trials of aspirin vs control in secondary prevention after TIA or ischemic stroke. N=15,778

- Aspirin reduced risk of disabling or fatal stroke by 80%
  - Most benefit in the 2 weeks following stroke
- Aspirin reduced recurrence by 60% at 6 weeks after stroke
- No reduction in risk after 12 weeks in aspirin group

Aspirin: Secondary Prevention

- Have we overestimated the importance of aspirin in long term secondary prevention?

- AHA/ACC Recommendation: for long term (>3 mo) secondary prevention
  - Aspirin monotherapy
  - Aspirin/Dipyridamole
    - Better long-term risk reduction than aspirin monotherapy
    - Caused more major bleeding than aspirin
  - Clopidigrel
    - Better long-term benefit than aspirin monotherapy?
    - Caused less major bleeding than aspirin

Antiplatelet Therapy After Noncardioembolic Stroke | Stroke (ahajournals.org) 2019

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 (ahajournals.org)

Aspirin Prevention of Ischemic Stroke: Summary

- Primary prevention: ASPREE, ARRIVE, USPTF
  - >60 y/o – No
  - 40-59 y/o Probably no
- Acute treatment: Definite recommendation for Aspirin (or DAPT)
  - Most important during the first 6 weeks after stroke
- Secondary prevention: Still recommended (for now)
  - ~14% reduction in recurrent stroke at 6 weeks
  - Risk reduction after 12 weeks?
  - Aspirin/dipyridamole and clopidogrel may be better

Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials - The Lancet

Long-term antithrombotic therapy for the secondary prevention of ischemic stroke - UpToDate

Is stopping aspirin in secondary prevention dangerous?

Effect of Discontinuing Aspirin Therapy on the Risk of Brain Ischemic Stroke | Cerebrovascular Disease | JAMA Neurology | JAMA Network

- Case control study; N=309
- Stopping aspirin as a risk factor for ischemic stroke
- 13 patients stopped aspirin within 4 weeks of stroke
- OR 3.4 ($p<0.005$)
- Stopping the aspirin increased risk of stroke

Aspirin for Prevention of Cardioembolic Stroke in Atrial Fibrillation

Case

Avery Fibrilator is an 85-year-old male you are admitting to your LTC facility. He has atrial fibrillation and is taking metoprolol and aspirin. He is able to make his own decisions and his mentation is excellent. He has had 3 falls over the last year with no significant injuries. He was living alone at home and his family checked in on him daily. He and his family have become concerned about his safety and have decided that LTC is his best option. They ask you to manage his medications using the best evidence-based information and are agreeable to any recommendations that you make.

What medication adjustments would you make?

A.) Continue aspirin for Afib related embolic stroke prevention

B.) Discontinue aspirin

C.) Discontinue aspirin and start apixaban

D.) Continue aspirin and add clopidogrel

Atrial Fibrillation in the Elderly

- Prevalence of ~4% of those > 60 years of age
- Afib increases stroke risk 5-fold
- Number of Afib related strokes increases with age
  - 1.5% at age 50 to 59
  - 2.8% at age 60 to 69
  - 9.9% at age 70 to 79
  - 23.5% at age 80 to 89

Overview of atrial fibrillation - UpToDate

Fall risk and anticoagulation for atrial fibrillation in the elderly: A delicate balance | Cleveland Clinic Journal of Medicine (ccjm.org)

Does Aspirin Prevent Afib Related Strokes?

Stroke Prevention in Atrial Fibrillation Study. Final results. | Circulation (ahajournals.org) – SPAF trial 1991

- Aspirin reduced Afib related strokes by 42%
- Warfarin reduced Afib related strokes by 67%

Meta-analysis: Antithrombotic Therapy to Prevent Stroke in Patients Who Have Nonvalvular Atrial Fibrillation | Annals of Internal Medicine (acpjournals.org) 2007

- Aspirin reduced Afib related strokes by **20%**
- Warfarin reduced Afib related strokes by 60%
- Aspirin has a larger effect on non-cardioembolic strokes than cardioembolic strokes

Bleeding Risk: Aspirin vs Warfarin

Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomized controlled trial - The Lancet 2007

- **Aspirin has the same bleeding risk as warfarin but is not as effective at preventing Afib related stroke.**
- Warfarin was superior in reducing thromboembolism risk
- Risk of major bleeding or intracranial hemorrhage was about the same

Bleeding Risk: Warfarin vs DOACs

DOACs are safer and noninferior to warfarin

Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation | NEJM

- Rivaroxaban was noninferior to warfarin for the prevention of stroke or systemic embolism

Apixaban versus Warfarin in Patients with Atrial Fibrillation | NEJM

- Apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality

Bleeding Risk: DOAC vs Aspirin

Thromboembolic Risk, Bleeding Outcomes and Effect of Different Antithrombotic Strategies in Very Elderly Patients With Atrial Fibrillation: A Sub-Analysis From the PREFER in AF (PREvention oF Thromboembolic Events; European Registry in Atrial Fibrillation) (nih.gov)

- **DOAC bleeding risk was not higher than that of patients receiving antiplatelet treatment**
- The older the patients with AF, the higher was the weighted net clinical benefit in favor of anticoagulant therapy

Effect of Age on Stroke Prevention Therapy in Patients With Atrial Fibrillation | Stroke (ahajournals.org)

- ***Aspirin becomes less effective at preventing stroke as we age but the bleeding risk stays the same***
- *DOAC efficacy is stable*

Misperceptions of aspirin efficacy and safety may perpetuate anticoagulant underutilization in atrial fibrillation | European Heart Journal | Oxford Academic (oup.com)

“Underutilization of OAC for AF may be perpetuated by aspirin remaining a soft option for physicians, based on misperceptions of both safety and efficacy of aspirin.”

Aspirin in Afib Summary

Aspirin no longer has a role in stroke prevention for Afib

- Aspirin reduced Afib related stroke risk 20%
- Warfarin reduces Afib related stroke risk 60%
- DOACS are noninferior to warfarin and probably safer
- Aspirin has the same bleeding risk as warfarin/DOACs
- Aspirin has significantly less efficacy compared to DOACs
- Aspirin is not safer in frail, elderly, Afib patients
- The European Society of Cardiology does not support antiplatelet monotherapy for stroke prevention irrespective of stroke risk.
- The 2019 AHA/ACC/HRS focused update omits any recommendation for aspirin in patients with low risk.

References

- Is It Time to Start Stopping Aspirin for Stroke Prevention in Afib? | MedPage Today
- Treating atrial fibrillation with antiplatelet drugs in the elderly: pro and contra arguments (escardio.org)
- Fall risk and anticoagulation for atrial fibrillation in the elderly: A delicate balance | Cleveland Clinic Journal of Medicine (ccjm.org)
- Misperceptions of aspirin efficacy and safety may perpetuate anticoagulant underutilization in atrial fibrillation | European Heart Journal | Oxford Academic (oup.com)

Aspirin in PAD/PVD

Aspirin in PAD/PVD

- Recs for Aspirin in PAD/PVD
  - Based on data from the Antithrombotic Trialists Collaboration 2002 and other similar studies
  - Goal is CVD risk reduction
- AHA/ACC Recs for PAD
  - Aspirin for primary prevention
  - Aspirin (or clopidigrel) for secondary prevention in symptomatic PAD
  - Aspirin (or clopidigrel) for secondary prevention in Asymptomatic PAD with low ABI is reasonable
- European guidelines
  - Against antiplatelet therapy in Asymptomatic PAD

Aspirin Monotherapy Should Not Be Recommended for Cardioprotection in Patients With Symptomatic Peripheral Artery Disease | Circulation (ahajournals.org)
ACC/AHA Versus ESC Guidelines for Diagnosis and Management of Peripheral Artery Disease: JACC Guideline Comparison - ScienceDirect

Aspirin in PAD/PVD

Newer studies looking specifically at PAD/PVD exist

- In patients with PAD, treatment with aspirin alone or with dipyridamole resulted in a statistically nonsignificant decrease in the primary end point of cardiovascular events and a significant reduction in nonfatal stroke. JAMA 2009
- In patients with no clinical CVD but with low ABI aspirin did not result in a significant reduction in vascular events. JAMA 2010

COMPASS Trial 2018

- Low dose rivaroxaban + aspirin and rivaroxaban monotherapy both reduced major adverse limb events.
- Increased bleeding with addition of rivaroxaban

Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial - PubMed (nih.gov)

Aspirin in PVD

Antithrombotic Therapy for Peripheral Artery Disease in 2018 | Cardiology | JAMA | JAMA Network

Antithrombotic Therapy for Peripheral Artery Disease in 2018

1. Confirm patient has peripheral artery disease (PAD) by vascular testing or history of prior lower extremity revascularization
2. Assess if patient has PAD-associated limb symptoms
3. Determine if patient has clinically manifest coronary artery disease (CAD) or cerebrovascular disease and if the patient has had an acute coronary syndrome or percutaneous coronary intervention within the past 12 mo or an acute cerebrovascular ischemic event

4. Select antithrombotic management

	PAD alone without clinically manifest CAD or cerebrovascular disease	PAD with clinically manifest CAD or cerebrovascular disease	
		No acute coronary syndrome or percutaneous coronary intervention within the past 12 mo or an acute cerebrovascular ischemic event	Acute coronary syndrome or percutaneous coronary intervention within the past 12 mo or an acute cerebrovascular ischemic event
Asymptomatic PAD	Do not initiate antithrombotic therapy Manage cardiovascular disease risk factors as indicated	**ANTITHROMBOTIC THERAPY FOR STABLE CARDIOVASCULAR DISEASE** Antithrombotic therapy, such as aspirin and/or oral P2Y12 inhibitor, according to current guidelines for treatment of stable CAD or cerebrovascular disease	**ANTITHROMBOTIC THERAPY FOR ACUTE CARDIOVASCULAR EVENT** Follow current guidelines for antithrombotic treatment of acute cardiovascular event
PAD-associated limb symptoms	**ANTITHROMBOTIC THERAPY FOR PAD** Clopidogrel or ticagrelor monotherapy to prevent MACE Evidence suggests clopidogrel is more effective than aspirin; ticagrelor is an acceptable alternative in patients known to be poor metabolizers of clopidogrel For patients with lower extremity revascularization, evidence supports aspirin monotherapy to maintain procedural patency	**ANTITHROMBOTIC THERAPY FOR PAD** Aspirin (or clopidogrel if aspirin is contraindicated) to prevent MACE For patients taking aspirin and at high risk of cardiac and ischemic limb events,[a] consider adding Ticagrelor if prior (> 12 mo ago) myocardial infarction to prevent MACE and MALE Low-dose reviroxaban if patient has concomitant CAD to prevent MACE and MALE[b] For patients at high risk of ischemic limb events, consider adding vorapaxar to aspirin or clopidogrel to prevent MALE[a]	

MACE indicates major adverse cardiac events (myocardial infarction, ischemic stroke, or cardiovascular death); MALE, major adverse limb events (acute limb ischemia or major amputation).

[a] Patients with PAD at highest risk for ischemic limb events are those with a prior history of lower extremity revascularization or more severe disease (ankle-brachial index <0.60).

[b] Rivaroxaban 2.5 mg twice daily for this indication is under review by the Food and Drug Administration but is not yet available in the United States.

Aspirin in PAD/PVD Summary

- Asymptomatic PAD without CVD
  - No aspirin
- Symptomatic PAD without CVD
  - Clopidogrel
  - Aspirin monotherapy after revascularization
- Asymptomatic PAD with CVD
  - Aspirin or clopidogrel based on CVD guidelines
- Symptomatic PAD with CVD
  - Aspirin
  - Consider adding rivaroxaban for those at high risk of critical limb ischemia

Antithrombotic Therapy for Peripheral Artery Disease in 2018 | Cardiology | JAMA | JAMA Network

Aspirin for Prevention Scorecard

Catagory	Aspirin		Notes
	Yes	No	
Primary Prevention CVD		x	Cardiovascular death, MI, CVA/TIA, PAD/PVD
STROKE			
Afib stroke prevention		x	DOACs have superior efficacy with bleeding risk similar to aspirin
Short-term Secondary prevention of ischemic stroke	++		Strong efficacy for first 6 weeks post stroke
Long-term Secondary prevention of ischemic stroke	?		Recommendations are to continue long term therapy Possibly diminishing returns after 12 weeks
PAD/PVD			
Asymptomatic PAD w/out CVD		x	
Symptomatic PAD w/out CVD		x	Clopidogrel preferred. Aspirin monotherapy reserved for after revascularization
Asymptomatic PAD with CVD	x		Aspirin or Clopidogrel based on CVD guidelines
Symptomatic PAD with CVD	x		Possible second agent for if high risk for critical limb ischemia

Case

Avery Fibrillator is an 85-year-old male you are admitting to your LTC facility. He has atrial fibrillation and is taking metoprolol and aspirin. He is able to make his own decisions and his mentation is excellent. He has had 3 falls over the last year with no significant injuries. He was living alone at home and his family checked in on him daily. He and his family have become concerned about his safety and have decided that LTC is his best option. They ask you to manage his medications using the best evidence-based information and are agreeable to any recommendations that you make.

What medication adjustments would you make?

A.) Continue aspirin for Afib related embolic stroke prevention

B.) Discontinue aspirin

C.) Discontinue aspirin and start apixaban

D.) Continue aspirin and add clopidogrel

Case

You perform a physical exam on Avery and note that he has no hair on his legs, cold feet, and bilaterally reduced peripheral pulses. He denies any claudication but admits to LE weakness and balance issues that he thinks have led to his falls over the last year. You dig through his records and find that he had doppler US ABIs done last year showing a RLE ABI or 0.8 and LLE ABI 0.9.
Does this change your answer?

What medication adjustments would you make?

A.) Continue aspirin for Afib related embolic stroke prevention
B.) Discontinue aspirin
C.) Discontinue aspirin and start apixaban
D.) Continue aspirin and add clopidogrel
E.) Discontinue aspirin and start clopidogrel
F.) Obtain LE CTA

Extra Slides

Aspirin for DVT prophylaxis

- Can we use Aspirin for DVT prophy in hip fracture with non-surgical management?

Aspirin for DVT prophylaxis after hip fracture surgery

Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial - PubMed (nih.gov)

- In a randomized trial of almost 18,000 patients, most of whom had hip fracture surgery/HFS, compared with placebo, aspirin administered for 35 days reduced the incidence of symptomatic DVT without an increase in major bleeding events but had no effect on the rate of clinically significant PE [98].

Intermittent Pneumatic Compression for the Prevention of Venous Thromboembolism after Total Hip Arthroplasty - PubMed (nih.gov) Clin Orthop Surg . 2017 Mar;9(1):37-42. doi: 10.4055/cios.2017.9.1.37. Epub 2017 Feb 13.

- In a randomized trial of 275 patients undergoing TKA, when used in combination with pneumatic compression devices, four weeks of aspirin had similar rates of DVT when compared with LMW heparin (18 versus 14 percent) [78]. In another trial in patients with THA, IPC devices in combination with six weeks of aspirin did not result in a significant reduction in rates of VTE compared with aspirin alone [136].

Association of Aspirin With Prevention of Venous Thromboembolism in Patients After Total Knee Arthroplasty Compared With Other Anticoagulants: A Noninferiority Analysis - PubMed (nih.gov) JAMA Surg. 2019 Jan 1;154(1):65-72.

- In a review of the Michigan Arthroplasty registry of over 41,000 patients undergoing TKA, the overall incidence of VTE was 1.38 percent [142]. The incidence was 4.79 percent among those who received no pharmacologic prophylaxis, 1.42 percent for those treated with anticoagulation alone (various agents and combinations), 1.31 percent for those prescribed both anticoagulation and aspirin, and **1.16 percent for those treated with aspirin alone**. Bleeding occurred in 1.10 percent of patients overall, and in 1.50, 1.35, 1.14 and **0.90** percent of the no prophylaxis, anticoagulation and aspirin, anticoagulation, and aspirin groups, respectively. Aspirin alone was noninferior for both the composite VTE outcome (unadjusted analysis) and for bleeding complications (unadjusted and adjusted analysis) compared with other nonaspirin treatment.

[Clinical Effectiveness and Safety of Aspirin for Venous Thromboembolism Prophylaxis After Total Hip and Knee Replacement: A Systematic Review and Meta-analysis of Randomized Clinical Trials | Orthopedics | JAMA Internal Medicine | JAMA Network] - Feb 3, 2020

Wide range of findings from RCTs. RCTs with Placebo control group excluded. Primary outcome was postoperative DVT.

No statistically significant difference between Aspirin and commonly used anticoagulants.

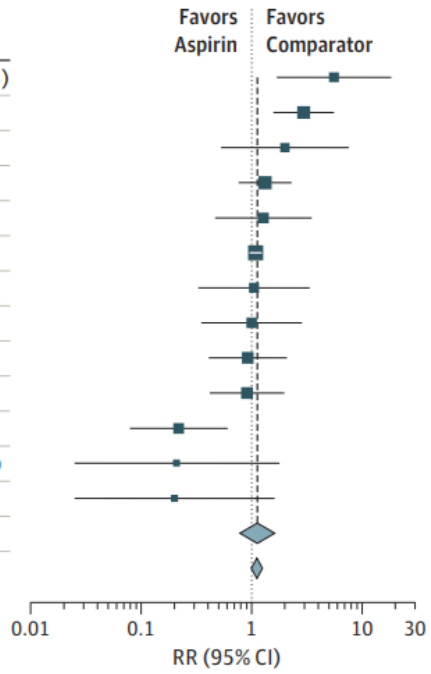
No significant difference in the risk of adverse events.

Most trials in the study had high rates of bias

The Anderson et al RCT gave 5 days of rivaroxiban prior to aspirin.

Figure 2. Effectiveness of Aspirin Compared With Other Anticoagulants on Venous Thromboembolism (Including Deep Vein Thrombosis and Pulmonary Embolism) in Randomized Clinical Trials of Patients Undergoing Total Hip and Knee Replacement

Source	Aspirin No. of Events	Aspirin No. of Participants	Comparator No. of Events	Comparator No. of Participants	RR (95% CI)	Weight, %
Zou et al,[26] 2014	18	110	3	102	5.56 (1.69-18.33)	5.89
Harris et al,[18] 1985	26	43	9	44	2.96 (1.57-5.55)	10.87
Kim et al,[21] 1998	6	50	3	50	2.00 (0.53-7.56)	5.10
Westrich et al,[24] 2006	24	129	19	135	1.32 (0.76-2.29)	11.79
Woolson et al,[25] 1991	8	72	6	69	1.28 (0.47-3.49)	7.21
Lotke et al,[22] 1996	131	166	106	146	1.09 (0.96-1.23)	15.87
Josefsson et al,[20] 1987	5	40	5	42	1.05 (0.33-3.35)	6.09
Salzman et al,[23] 1971	6	43	6	43	1.00 (0.35-2.86)	6.87
Anderson et al,[9] 2018	11	1707	12	1717	0.92 (0.41-2.08)	8.91
Jiang et al,[19] 2014	10	60	11	60	0.91 (0.42-1.98)	9.29
Gelfer et al,[17] 2006	4	61	18	60	0.22 (0.08-0.61)	7.10
Anderson et al,[11] 2013	1	380	5	398	0.21 (0.02- 1.78)	2.45
Alfaro et al,[27] 1986	1	30	5	30	0.20 (0.02-1.61)	2.56
Random effects					1.12 (0.78-1.62)	100.00
Fixed effects					1.11 (0.99-1.25)	



Thirteen randomized clinical trials[9,11,17-27] were included. Outcomes included both symptomatic and asymptomatic venous thromboembolism events. The summary estimate presented was calculated using a random-effects model. Sizes of data markers are proportional to the inverse of the variance of the relative ratio. RR indicates relative risk. The diamonds represent the overall estimated relative risk (with 95% CIs) for the 13 trials combined when using a random-effects model and when using a fixed-effects model.

Aspirin in healthy individuals to modify VTE risk

Effect of low-dose aspirin on the occurrence of venous thromboembolism: a randomized trial - PubMed (nih.gov)

- In the Women's Health Study, VTE rates were no different in healthy females that were randomly assigned to receive either low-dose aspirin (100 mg orally every other day) or placebo for 10 years (1.18 versus 1.25 events per 1000 patient-years) [60]. On subgroup analysis, no VTE risk factor (ie, age, obesity, menopausal status, reported VTE at baseline, factor V Leiden, prothrombin gene mutation) modified the relationship between aspirin and the overall risk of VTE. However, the use of aspirin was associated with an increased risk of gastrointestinal bleeding, peptic ulcer, hematuria, bruising, and epistaxis.

- Lower Extremity Peripheral Artery Disease: AHA Scientific Statement - American College of Cardiology (acc.org)

- Of Life and Limb: Addition of Low-Dose Rivaroxaban for Secondary Prevention After Peripheral Artery Disease Surgery | Circulation (ahajournals.org)
  - compared CAD+PAD patients, patients with PAD only are less likely to receive antiplatelet drugs, statins, or smoking-cessation interventions

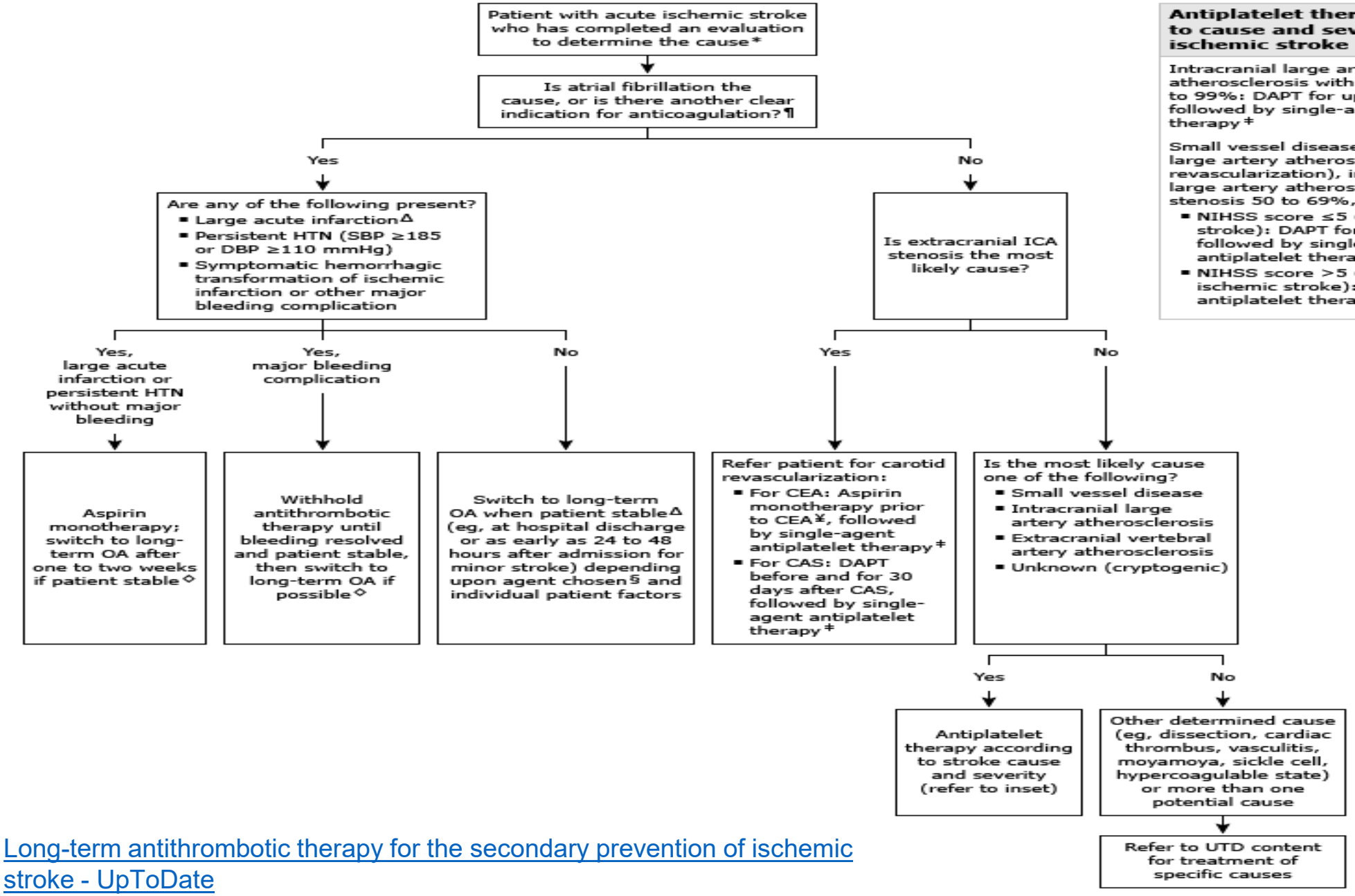
Antiplatelet Therapy After Noncardioembolic Stroke - PubMed (nih.gov) 2019

- network meta-analysis (NMA) of data from 6 randomized trials of the effects of commonly prescribed antiplatelet agents in the long-term (≥3 months) secondary prevention of noncardioembolic stroke or transient ischemic attack.
- Aspirin/dipyridamole combination ($RR_{NMA-adj}$, 0.83; 95% CI, 0.74-0.94) significantly reduced the risk of vascular events compared with aspirin, as did clopidogrel ($RR_{NMA-adj}$, 0.88; 95% CI, 0.78-0.98), and aspirin/clopidogrel combination ($RR_{NMA-adj}$, 0.83; 95% CI, 0.71-0.96)
- Clopidogrel caused significantly less major bleeding and intracranial hemorrhage than aspirin, aspirin/dipyridamole combination, and aspirin/clopidogrel combination.
- Net clinical benefit was similar for clopidogrel and aspirin/dipyridamole combination ($RR_{NMA-adj}$, 0.99; 95% CI, 0.93-1.05).
- The excess risk of major bleeding associated with aspirin/clopidogrel combination compared with clopidogrel alone was higher in patients aged <65 years than it was in patients ≥65 years ($RR_{NMA-adj}$, 3.9 versus 1.7).
- Conclusions- Results favor clopidogrel and aspirin/dipyridamole combination for long-term secondary prevention after noncardioembolic stroke or transient ischemic attack, regardless of patient characteristics. Aspirin/clopidogrel combination was associated with a significantly higher risk of major bleeding compared with other antiplatelet regimens.

- **Risk of stopping antiplatelet treatment** — Stopping antiplatelet therapy in high-risk patients may itself increase the risk of stroke. One study found that 13 of 289 patients hospitalized with cerebral infarction had recently stopped antiplatelet therapy; most had been taking aspirin [6]. In all 13, the antiplatelet agent had been discontinued within 6 to 10 days of stroke onset, a time course consistent with the known lifespan (about 10 days) of inhibited platelets. Additionally, a case-control study comparing 309 patients with stroke to 309 matched controls found that discontinuation of aspirin was associated with a significantly increased risk of TIA or ischemic stroke (odds ratio 3.4, 95% CI 1.08-10.63) [7].

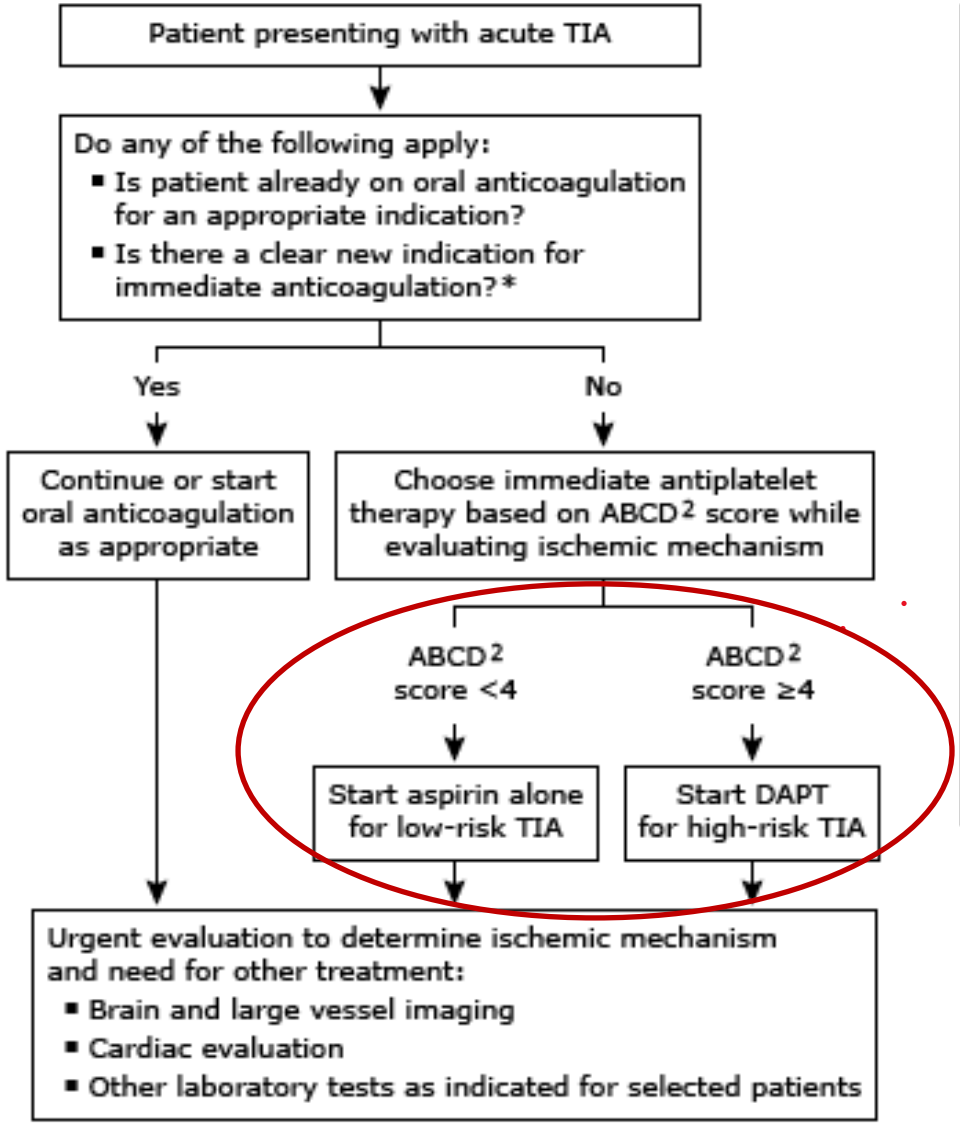
Long-term antithrombotic therapy for the secondary prevention of ischemic stroke - UpToDate

Antithrombotic therapy according to cause of acute ischemic stroke



[Long-term antithrombotic therapy for the secondary prevention of ischemic stroke - UpToDate]

Immediate antithrombotic treatment of transient ischemic attack (TIA)



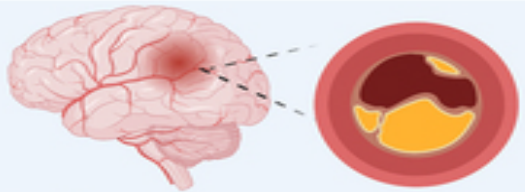
ABCD^2 score	
Age:	
≥60 years	+1
<60 years	0
BP at TIA presentation:	
SBP ≥140 or DBP ≥90	+1
SBP <140 and SBP <90	0
Clinical features:	
Unilateral weakness	+2
Isolated speech disturbance	+1
Other	0
Duration of TIA symptoms:	
≥60 minutes	+2
10 to 59 minutes	+1
<10 minutes	0
Diabetes:	
Present	+1
Absent	0

ABCD^2: age, blood pressure, clinical features, duration of symptoms, and diabetes; DAPT: dual antiplatelet therapy (eg, aspirin and clopidogrel, or aspirin and ticagrelor); BP: blood pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure.

* Indications for long-term oral anticoagulation include embolism prevention for patients with atrial fibrillation, ventricular thrombus, mechanical heart valve, and treatment of venous thromboembolism.

Dual Antiplatet Therapy Versus Aspirin in Minor Stroke or TIA

Meta-Analysis of Randomized Controlled Trials



4 trials, 21,459 patients with minor stroke or high-risk TIA

	Aspirin + P2Y12i	Aspirin + Placebo
	N = 10,737	N = 10,722
Recurrent Stroke (N)	626	827
	RR 0.76; 95% CI, 0.68-0.83; P <0.001	
Major Bleed (N)	71	29
	RR 2.2; 95% CI, 1.14-4.34; P =0.02	

In minor stroke or high-risk TIA, short term DAPT reduced the risk of recurrent stroke at the expense of a higher risk of major bleeds

Kirtipal Bhatia. Stroke. Dual Antiplatelet Therapy Versus Aspirin in Patients With Stroke or Transient Ischemic Attack: Meta-Analysis of Randomized Controlled Trials, Volume: 52, Issue: 6, Pages: e217-e223, DOI: (10.1161/STROKEAHA.120.033033)

1. Do we need to use plavix with aspirin in CVA?

Interesting facts

- Enteric coated aspirin does not protect against GI bleeding.
  - Risk of aspirin-associated major upper-gastrointestinal bleeding with enteric-coated or buffered product - PubMed (nih.gov)

Antithrombotic Trialists Collaboration

Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients (nih.gov)

- 2002 meta-analysis from Antithrombotic Trialists Collaboration included 195 randomized controlled trials of high-risk patients
- Primary prevention: **25% RRR in nonfatal stroke compared to placebo**
- Secondary prevention: 22% reduction
- Benefit independent of age, diabetes, hypertension, sex
- Low dose as effective as higher doses

Long-term antithrombotic therapy for the secondary prevention of ischemic stroke - UpToDate

Bleeding risks with novel oral anticoagulants especially rivaroxaban versus aspirin: a meta-analysis – Oct 2021

- The bleeding risks associated with NOACs depend on drug type and dosage. For ≥15 mg/day of rivaroxaban, the risk of ICH was significantly higher than that with aspirin. However, further studies comparing dabigatran etexilate and apixaban versus aspirin are warranted to draw a definite conclusion.

Bleeding risks with novel oral anticoagulants especially rivaroxaban versus aspirin: a meta-analysis | Thrombosis Journal | Full Text (biomedcentral.com)

Aspirin for CVA prevention

Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients (nih.gov) – 1/12/2002

- 2002 meta-analysis from Antithrombotic Trialists Collaboration included 195 randomized controlled trials of high risk patients
- Primary prevention: **25% RRR in nonfatal stroke compared to placebo (p<0.0001)**
- Secondary prevention: 22% reduction
- Benefit independent of sex, age, diabetes, hypertension
- Low dose as effective as higher doses.

So it is good for primary prevention? Right?

Aspirin for CVA prevention

Aspirin for the Primary Prevention of Cardiovascular Events: A Systematic Evidence Review for the U.S. Preventive Services Task Force - PubMed (nih.gov) -- 2016

- Aspirin has no significant benefit on non-fatal stroke
  - RR 0.95, 95% CI 0.85-1.06

Aspirin use in endovascular stroke treatment.

MR CLEAN-MED Trial

Safety and efficacy of aspirin, unfractionated heparin, both, or neither during endovascular stroke treatment (MR CLEAN-MED): an open-label, multicentre, randomised controlled trial - The Lancet

Interpretation

- Periprocedural intravenous aspirin and unfractionated heparin during endovascular stroke treatment are both associated with an increased risk of symptomatic intracranial haemorrhage without evidence for a beneficial effect on functional outcome.

DAPT for CVA

Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events - PubMed (nih.gov)

- RCCT, 15,603 patients with either clinically evident cardiovascular disease or multiple risk factors to receive clopidogrel (75 mg per day) plus low-dose aspirin (75 to 162 mg per day) or placebo plus low-dose aspirin and followed them for a median of 28 months.
- Overall, **clopidogrel plus aspirin was not significantly more effective than aspirin alone** in reducing the rate of myocardial infarction, stroke, or death from cardiovascular causes.

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 - The Lancet

- Adding aspirin to clopidogrel in high-risk patients with recent ischaemic stroke or transient ischaemic attack is associated with a non-significant difference in reducing major vascular events. However, the risk of life-threatening or major bleeding is increased by the addition of aspirin.

Effects of clopidogrel added to aspirin in patients with recent lacunar stroke - PubMed (nih.gov)

- Double blind, multicenter trial, n=3020, pts with recent lacunar infarcts.
- Among patients with recent lacunar strokes, the addition of clopidogrel to aspirin did not significantly reduce the risk of recurrent stroke and did significantly increase the risk of bleeding and death.