ASPIRIN FOR PRIMARY PREVENTION AND LANDMARK EVIDENCE

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I THE PARADIGM SHIFT: FROM UNIVERSAL USE TO SELECTIVE BLEEDING AVOIDANCE

- **Historical Context vs. Modern Reality:** Early primary-prevention aspirin trials conducted in the 1980s and 1990s (**Physicians' Health Study, HOT, Thrombosis Prevention Trial**) enrolled cohorts with high smoking rates, untreated blood pressure, and minimal statin use. In the contemporary era of widespread **high-intensity statin therapy, strict blood pressure control, and declining smoking rates**, baseline incident ASCVD event rates have fallen substantially.
- **The Neutralized Net Clinical Benefit:** While low-dose Aspirin (75 to 100 mg daily, irreversibly acetylating platelet **COX-1** at Serine-529 to block **Thromboxane A2** synthesis) produces a modest **10 to 12 percent relative risk reduction** in non-fatal ischemic events, it simultaneously causes a **30 to 50 percent relative increase in major gastrointestinal and intracranial hemorrhage** (by inhibiting gastric mucosal cytoprotective prostaglandin E2/prostacyclin). In low-to-moderate risk primary prevention, the **Number Needed to Treat (NNT) to prevent one ischemic event approximates or exceeds the Number Needed to Harm (NNH) to cause one major bleed**, eliminating net clinical benefit and zeroing out any all-cause or cardiovascular mortality reduction.

II CONTEMPORARY GUIDELINE RECOMMENDATIONS (ACC/AHA 2019, ESC 2021, AND USPSTF 2022)

Guideline Body	Target Age & Clinical Group	Class / Grade of Recommendation	Specific Clinical Guidance
2019 ACC/AHA Primary Prevention Guidelines	**Adults Aged 40 to 70 Years** at **Higher ASCVD Risk** & **NO Increased Bleeding Risk**	**Class IIb (Level A)** — *May Be Considered*	Low-dose Aspirin (75–100 mg/d) may be considered selectively in higher-risk adults (e.g., 10-yr ASCVD risk >=10–20%, **CAC >=100**, or uncontrolled risk factors)
2019 ACC/AHA Primary Prevention Guidelines	**Adults Aged >70 Years** (Routine Primary Prevention)	**Class III: Harm (Level B-R)** — *Do Not Administer*	Routine low-dose Aspirin is contraindicated for primary prevention in adults >70 years old (**ASPREE Trial**)
2019 ACC/AHA Primary Prevention Guidelines	**Adults of ANY Age at Increased Risk of Bleeding**	**Class III: Harm (Level C-LD)** — *Do Not Administer*	Contraindicated in prior GI bleed/peptic ulcer, thrombocytopenia, coagulopathy, CKD, or concurrent **NSAIDs, steroids, or anticoagulants**
2022 USPSTF Recommendation	**Adults Aged 40–59 Years** (>=10% 10-yr risk) vs. **Adults >=60 Years**	**Grade C** (Age 40–59 yr); **Grade D — Against Initiating** (Age **>=60 yr**)	Individualized shared decision at age 40–59 yr; **do not initiate** primary-prevention aspirin at **age 60 years or older**
2021 ESC Prevention / 2023 ESC Diabetes Guidelines	**Diabetes Mellitus Without Symptomatic ASCVD**	**Class IIb (Level A)** in High/Very-High Risk DM; **Class III** in Low/Moderate Risk	Aspirin (75–100 mg/d) may be considered in DM at high/very-high risk in the absence of clear contraindications (**ASCEND Trial**)

III THE 2018 LANDMARK "EVIDENCE TRINITY" (ARRIVE, ASCEND, AND ASPREE TRIALS)

- **The ARRIVE Trial (*Lancet* 2018 — Moderate-Risk Non-Diabetic Adults):**
- **Population and Design:** Randomized 12,546 **non-diabetic** adults (men >=55 yr, women >=60 yr) with an estimated moderate 10-year cardiovascular risk (10 to 20 percent; actual observed 10-year event rate was lower at ~8 to 9 percent due to contemporary BP/statin therapy) to enteric-coated **Aspirin 100 mg daily vs. Placebo** for a median of 5 years.
- **Results:** Aspirin **did NOT reduce the primary composite endpoint** of CV death, MI, unstable angina, stroke, or TIA (**4.29 percent vs. 4.48 percent; HR 0.96; p = 0.60**), while **more than doubling gastrointestinal bleeding (0.97 percent vs. 0.46 percent; HR 2.11; p = 0.0007)**.
- **The ASCEND Trial (*NEJM* 2018 — Primary Prevention in Diabetes Mellitus):**
- **Population and Design:** Randomized 15,480 adults (aged >=40 years) with **Diabetes Mellitus and no evident cardiovascular disease** to **Aspirin 100 mg daily vs. Placebo** for a mean of 7.4 years.
- **Results:** Aspirin significantly **reduced serious vascular events by 12 percent (8.5 percent vs. 9.6 percent; Rate Ratio 0.88; p = 0.01; absolute risk reduction 1.1 percent)**; however, it simultaneously **increased major bleeding events by 29 percent (4.1 percent vs. 3.2 percent; Rate Ratio 1.29; p = 0.003; absolute risk increase 0.9 percent)**—meaning the **absolute ischemic reduction (NNT = 91) was almost completely counterbalanced by the absolute major bleeding increase (NNH = 112)**.
- **The ASPREE Trial (*NEJM* 2018 — Healthy Older Adults Aged >=70 Years):**
- **Population and Design:** Randomized 19,114 healthy community-dwelling older adults (**aged >=70 years**, or >=65 years among US Black and Hispanic participants) free of cardiovascular disease, dementia, or physical disability to **Aspirin 100 mg daily vs. Placebo** for a median of 4.7 years.
- **Results:** Aspirin **failed to prolong disability-free survival** (the primary composite of death, dementia, or persistent physical disability) and **failed to significantly reduce cardiovascular disease (HR 0.95)**, while causing a **38 percent relative increase in major hemorrhage (3.8 percent vs. 2.8 percent; HR 1.38; p < 0.001, including higher intracranial bleeding)** and an unexpected **higher all-cause mortality (5.9 percent vs. 5.2 percent; HR 1.14)**, a secondary finding to be interpreted with caution, driven mainly by cancer-related deaths in this elderly cohort.

IV CORONARY ARTERY CALCIUM (CAC) AS THE IMAGING TIE-BREAKER AND THE INDIAN CONTEXT

- **The MESA CAC Tie-Breaker Rule (Cainzos-Achirica et al., *Circulation* 2020):** In asymptomatic primary-prevention adults aged 40 to 70 years without high bleeding risk, **Coronary Artery Calcium (CAC) scoring** accurately separates those harmed versus helped by Aspirin:
- **CAC = 0 (and CAC 1 to 99):** The 10-year number needed to harm from major bleeding is far lower than the number needed to treat (**Net Harm**); **Aspirin should be strictly withheld when CAC = 0**.
- **CAC >= 100 Agatston Units (and Especially CAC >= 300 or >= 400):** Signifies substantial subclinical atherosclerotic plaque burden where the absolute 5-year MACE reduction exceeds the major bleeding risk (**Net Clinical Benefit**), making low-dose Aspirin (75 to 100 mg/day) a **reasonable (Class IIb) addition to high-intensity statin therapy**.
- **Elevated Lipoprotein(a) Subgroup (ASPREE & Women's Health Study Genotyping):** Post-hoc genetic analyses suggest that primary-prevention individuals carrying high-risk *LPA* genotypes or **severely elevated Lipoprotein(a) (>50 to 70 mg/dL)** may derive a significant reduction in MACE from low-dose Aspirin without net harm.
- **Practical Application in the Indian Clinical Context:**
  - **Avoiding Reflex Aspirin in Uncomplicated Diabetes:** Despite the high prevalence of Type 2 Diabetes in India, **routine Aspirin is NOT indicated based on diabetes alone**; foundational primary prevention in Indian diabetics relies on **High-Intensity Statins, SGLT2 Inhibitors, GLP-1 Receptor Agonists, and Blood Pressure Control**.
  - **High Endemic *H. pylori* and OTC NSAID GI Bleeding Risk:** Because Indian patients have a high prevalence of *Helicobacter pylori* gastritis/peptic ulcer disease and frequent unmonitored use of over-the-counter NSAIDs, **co-prescription of a Proton Pump Inhibitor (PPI)** should be considered whenever low-dose Aspirin is initiated in high-risk primary-prevention patients (e.g., age 40 to 59 years with **CAC >=100** or non-obstructive plaque on CCTA).

KEY REFERENCES

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- **McNeil JJ, Wolfe R, Woods RL, et al. (ASPREE Investigator Group):** Effect of Aspirin on Cardiovascular Events and Bleeding in the Healthy Elderly, *New England Journal of Medicine*, 2018.