ASPIRIN IN PRIMARY PREVENTION: CURRENT STATUS

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Last reviewed: October 2026

I INTRODUCTION AND THE CONTEMPORARY RISK-BENEFIT SHIFT

- **The Narrowed Therapeutic Window:** Low-dose Aspirin (75 to 100 mg once daily) irreversibly inhibits platelet cyclooxygenase-1 (**COX-1**), suppressing prothrombotic **Thromboxane A2** generation for the 7-to-10-day lifespan of the platelet. While Aspirin remains an indisputable **Class I cornerstone in secondary prevention** (prior MI, PCI, CABG, or ischemic stroke), its role in **primary prevention** has been sharply curtailed.
- **Why the Paradigm Changed:** Widespread adoption of **high-intensity statins, modern antihypertensives, SGLT2 inhibitors/GLP-1 receptor agonists, and smoking cessation** has lowered baseline first-time ASCVD event rates by 40 to 50 percent over the past three decades; consequently, the small absolute reduction in non-fatal MI (~1 to 2 events per 1,000 patient-years) is matched or exceeded by the absolute increase in **major gastrointestinal and intracranial bleeding** (~1 to 2 events per 1,000 patient-years), with **zero reduction in cardiovascular or all-cause mortality**.

II CURRENT CLINICAL GUIDELINE RECOMMENDATIONS

- **Adults Aged 40 to 59 Years (USPSTF 2022 Grade C) / 40 to 70 Years (ACC/AHA 2019 Class IIb):** Low-dose Aspirin (75 to 100 mg daily) **may be considered selectively** via shared decision-making **only** in individuals with a **high 10-year ASCVD risk (10 percent or greater; >20 percent in many consensus algorithms)** who have **low bleeding risk** and subclinical atherosclerosis modifiers (such as **Coronary Artery Calcium [CAC] score >=100 Agatston units** or elevated Lipoprotein(a)).
- **Older Adults — Age >=60 Years (USPSTF 2022 Grade D) and Age >70 Years (ACC/AHA 2019 Class III: Harm):** Routine initiation of low-dose Aspirin for primary prevention is **not recommended at age 60 years or older** and is **contraindicated (Class III: Harm) in adults over 70 years of age**, because major extracranial and intracranial bleeding risk rises exponentially with age and outweighs any ischemic benefit.
- **Any Age with Increased Bleeding Risk (ACC/AHA Class III: Harm):** Strictly contraindicated in patients with prior peptic ulcer disease or GI hemorrhage, anemia, thrombocytopenia, chronic kidney disease, chronic liver disease, uncontrolled hypertension, or concomitant use of **NSAIDs, corticosteroids, or oral anticoagulants**.
- **Diabetes Mellitus Without Established ASCVD (ESC 2023 Class IIb):** Diabetes alone is **not** an automatic indication for Aspirin; low-dose Aspirin (75 to 100 mg/day) may be considered (Class IIb) only in diabetic patients at **high or very-high cardiovascular risk** (e.g., long diabetes duration >=10 years with target-organ damage or multiple risk factors) in the absence of bleeding contraindications.

III THE THREE LANDMARK 2018 RANDOMIZED TRIALS

Landmark Trial (2018)	Target Population & Sample Size	Primary Efficacy Outcome (Ischemic Events)	Primary Safety Outcome (Major Bleeding)	Definitive Clinical Verdict
ARRIVE (*Lancet* 2018)	**12,546 Moderate-Risk Non-Diabetic Adults** (men >=55 yr, women >=60 yr)	**Neutral:** 4.29% vs. 4.48% (**HR 0.96**; p = 0.60)	**2.1-fold increase in GI bleeding** (0.97% vs. 0.46%; **HR 2.11**)	**Ineffective** in moderate-risk non-diabetic primary prevention
ASCEND (*NEJM* 2018)	**15,480 Adults with Diabetes Mellitus** (>=40 yr) and no baseline CVD	**12% RRR** in serious vascular events (8.5% vs. 9.6%; **ARR 1.1%**, NNT = 91)	**29% increase** in major bleeding (4.1% vs. 3.2%; **ARI 0.9%**, NNH = 112)	Ischemic benefit **offset by major bleeding**; not routine for all diabetics
ASPREE (*NEJM* 2018)	**19,114 Healthy Elderly Adults** (**>=70 yr**, or >=65 yr US Black/Hispanic)	**No benefit** on disability-free survival or MACE (**HR 0.95**)	**38% increase in major hemorrhage** (**HR 1.38**) + **higher all-cause mortality (HR 1.14)**	**Harmful (Class III)** in healthy elderly >=70 years

IV PRECISION IMAGING GUIDANCE AND THE INDIAN CLINICAL CONTEXT

- **Coronary Artery Calcium (CAC)-Guided Aspirin Allocation:** Because clinical risk calculators poorly discriminate true plaque burden, **CAC scoring** serves as the premier tie-breaker in borderline/intermediate-risk patients aged 40 to 60 years:
- **CAC = 0:** Very low 10-year event rate (<1% to 1.5%); **Aspirin causes net harm and is avoided**.
- **CAC >= 100 Agatston Units (or Non-Obstructive Plaque on Coronary CTA):** Identifies patients with established subclinical coronary atherosclerosis who achieve a favorable net reduction in myocardial infarction from **Aspirin 75 mg/day + High-Intensity Statin** (provided bleeding risk is low).
- **Targeted Application in the Indian Phenotype:** Recognizing that South Asians develop premature CAD a decade earlier than Western populations, Indian expert practice favours reserving primary-prevention Aspirin for **adults under 60 years of age with very high lifetime risk**—specifically those with **CAC >=100**, **familial hypercholesterolemia**, **severely elevated Lipoprotein(a) (>50 mg/dL)** with multiple risk factors, or **high-risk diabetes with microangiopathy**—while routinely co-prescribing gastroprotection when indicated due to high endemic *H. pylori* prevalence.

KEY REFERENCES

- **Arnett DK, Blumenthal RS, Albert MA, et al.:** 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease, *Circulation*, 2019.
- **US Preventive Services Task Force (Davidson KW, Barry MJ, Mangione CM, et al.):** Aspirin Use to Prevent Cardiovascular Disease: US Preventive Services Task Force Recommendation Statement, *JAMA*, 2022.
- **Cainzos-Achirica M, Miedema MD, McEvoy JW, et al.:** Coronary Artery Calcium for Personalized Allocation of Aspirin in Primary Prevention of Cardiovascular Disease in 2019: The MESA Study, *Circulation*, 2020.