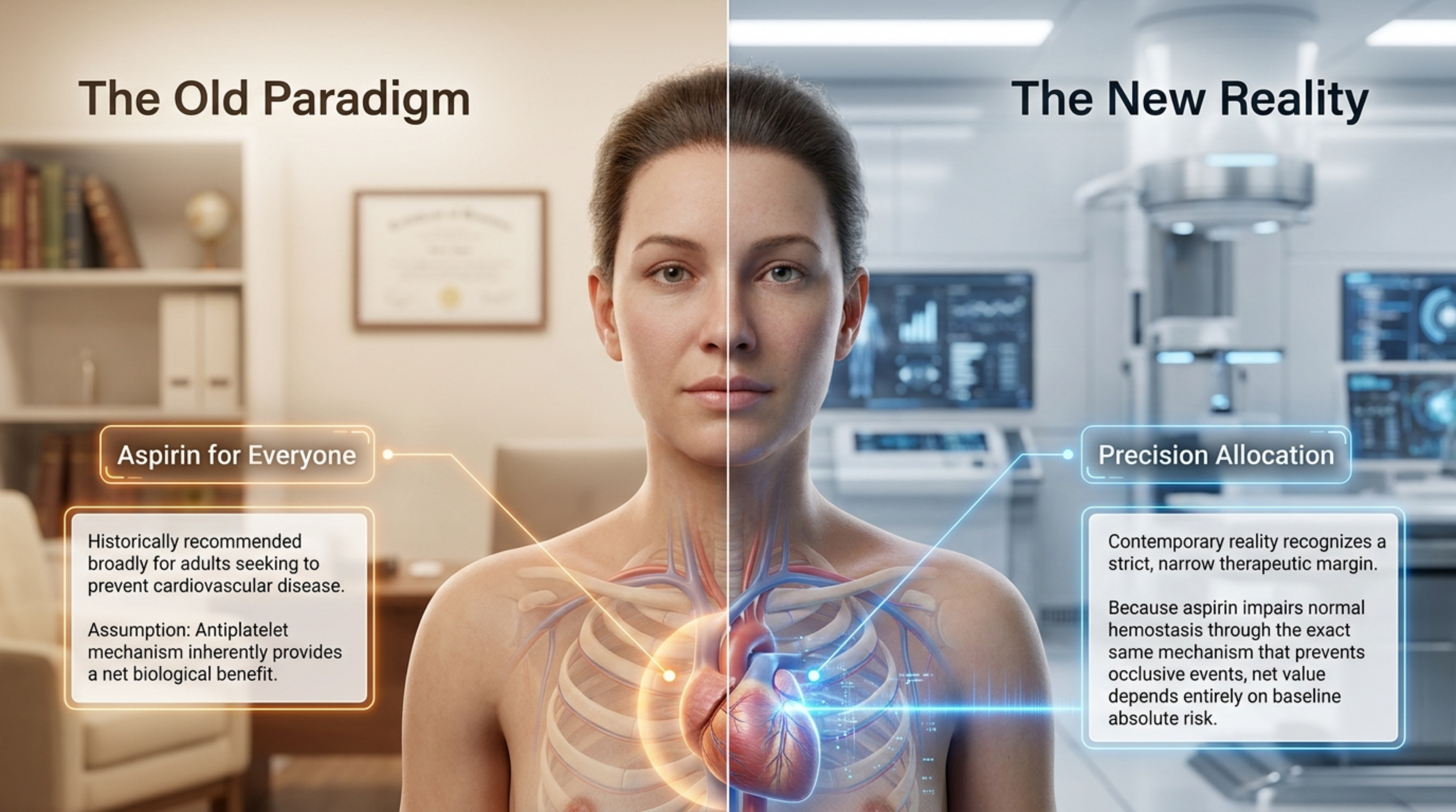
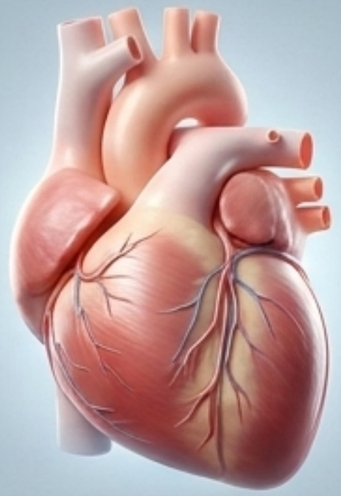
The Narrow Margin: Aspirin in Cardiovascular Prevention

An Evidence-Based Atlas of Efficacy, Safety, Dose-Response, and Patient-Specific Stratification.

Synthesized from the 2022 USPSTF, 2019 ACC/AHA Primary Prevention, and 2025 ACC/AHA ACS Guidelines.


The Old Paradigm
The New Reality
Aspirin for Everyone
Historically recommended broadly for adults seeking to prevent cardiovascular disease.
Assumption: Antiplatelet mechanism inherently provides a net biological benefit.
Precision Allocation
Contemporary reality recognizes a strict, narrow therapeutic margin.
Because aspirin impairs normal hemostasis through the exact same mechanism that prevents occlusive events, net value depends entirely on baseline absolute risk.

Primary Prevention
(No Evident Disease)



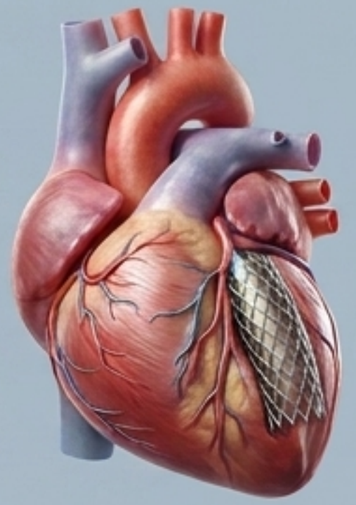
- **Baseline Risk**: Low absolute annual event rate.

- **Ischemic Benefit:** Minimal (ATT Meta-analysis: ~0.06% per-year absolute reduction in serious vascular events).

- **Bleeding Hazard:** Largely offsets ischemic benefit (GI and intracranial hemorrhage).

- **Contemporary Action**: Routine use abandoned. Highly individualized.

Secondary Prevention
(Established Disease)



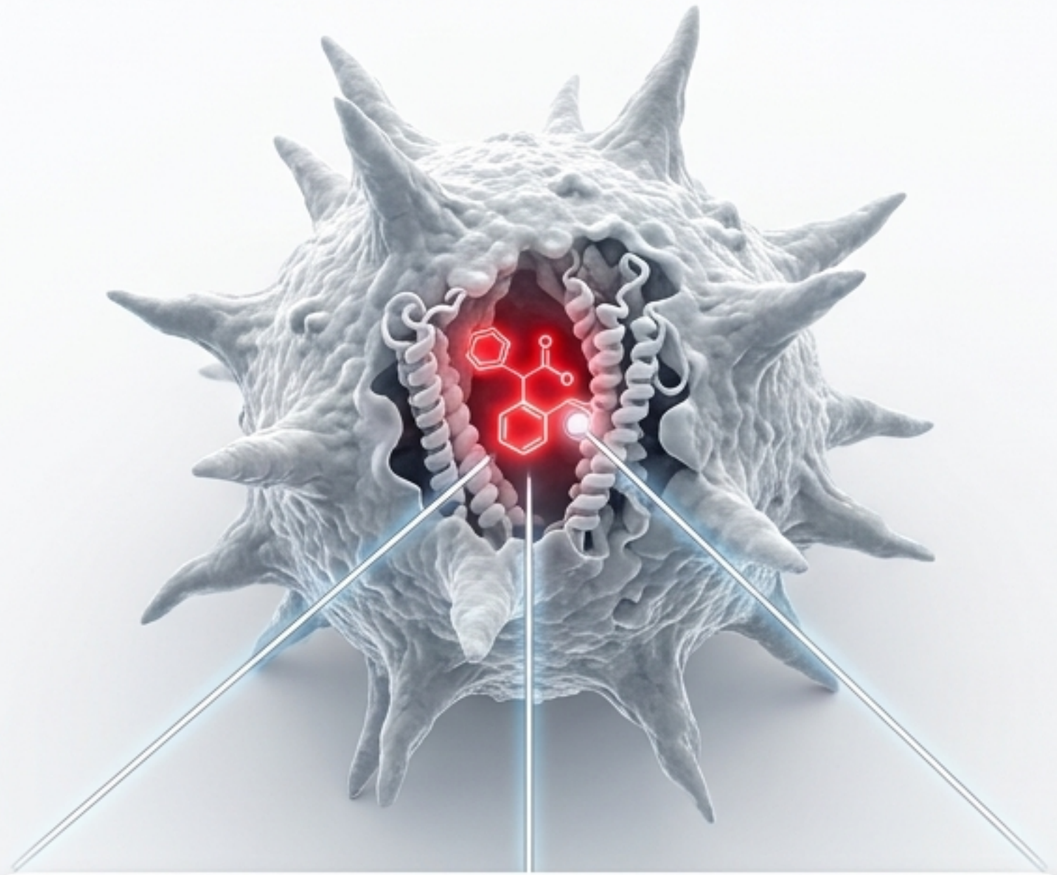
- **Definition**: Prior MI, stroke, TIA, angina, PAD, or revascularization.

- **Baseline Risk**: High absolute risk of recurrent thrombotic events.

- **Ischemic Benefit:** Large absolute benefit that decisively outweighs bleeding.

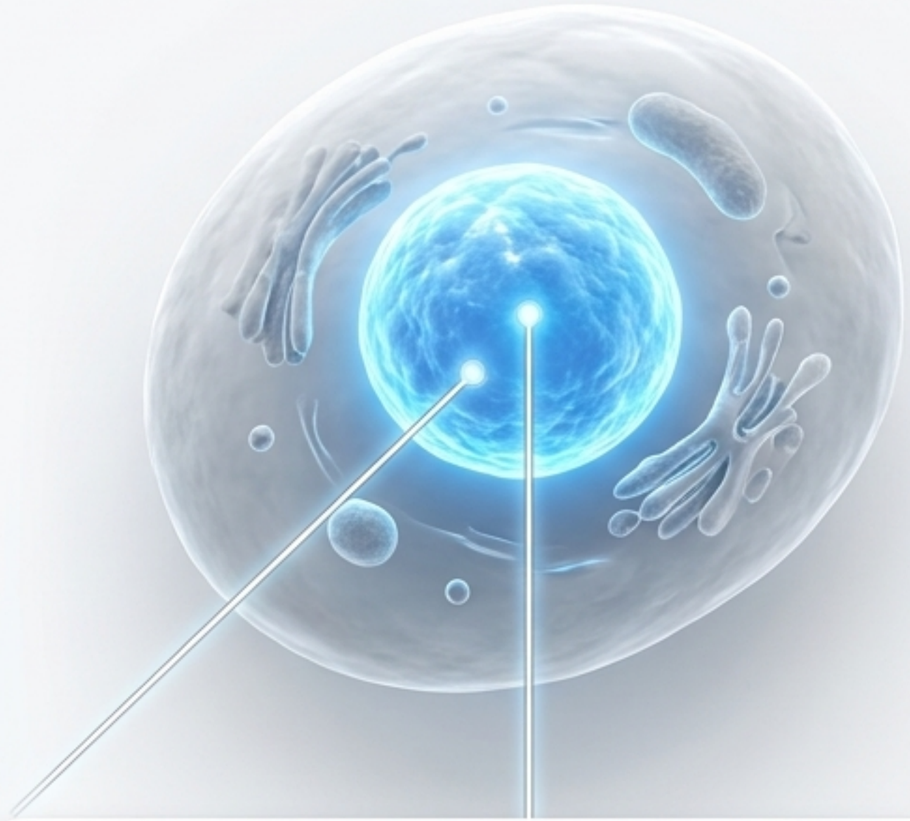
- **Contemporary Action:** Continue 81mg daily (2023 AHA/ACC Class 1, LOE A).

Platelet Response (TxA2)



Irreversible Blockade: Aspirin acetylates Ser-530, permanently halting synthesis of prostanoid thromboxane A2 (TxA2). Because platelets are anucleate, COX-1 blockade persists for their entire 7-10 day lifespan despite aspirin's 20-minute plasma half-life.

Endothelial Response (PGI2)



Endothelial Regeneration: Endothelial cells are nucleated and resynthesize cyclooxygenase to produce prostacyclin (PGI2), a vasodilator. Low doses (75-100 mg) suppress platelet TxA2 while relatively sparing endothelial PGI2.

The Turnover Constraint

Dosing interval is strictly constrained by marrow turnover. New, uninhibited platelets enter circulation daily.

Daily vs. Alternate Dosing

Once-daily dosing is required to maintain steady-state inhibition. The Women's Health Study showed 100mg every other day failed to significantly reduce major cardiovascular events—pharmacodynamic off-day gaps allow newly formed platelets to restore thromboxane capacity.

ADAPTABLE Trial Results

15,076 patients with established ASCVD. Over 26.2 months, composite death/MI/stroke hospitalization showed no significant difference (7.28% for 81mg vs 7.51% for 325mg). Major bleeding hospitalization also showed no significant difference.

The Crossover Caveat

Asymmetric crossover biases toward the null. 41% of patients assigned to 325mg switched to 81mg; only 7% switched the other way.

Guideline Consensus: 81mg is the preferred maintenance dose. It provides near-maximal platelet inhibition, comparable clinical protection, and better tolerability. Higher doses are reserved strictly for acute loading.

Ischemic Events Prevented

Modest proportional reduction in serious vascular events. In primary prevention, this translates to a minimal ~0.06% per-year absolute reduction (ATT Meta-analysis).

Bleeding Hazard Initiated

Impaired hemostasis causes parallel absolute increases in major bleeding—principally gastrointestinal and intracranial hemorrhage.

In populations without documented cardiovascular disease, the absolute bleeding excess almost perfectly offsets the small absolute ischemic benefit.

ASCEND Trial Cohort

15,480 adults with diabetes, no known cardiovascular disease.
100mg daily vs placebo (7.4 years).

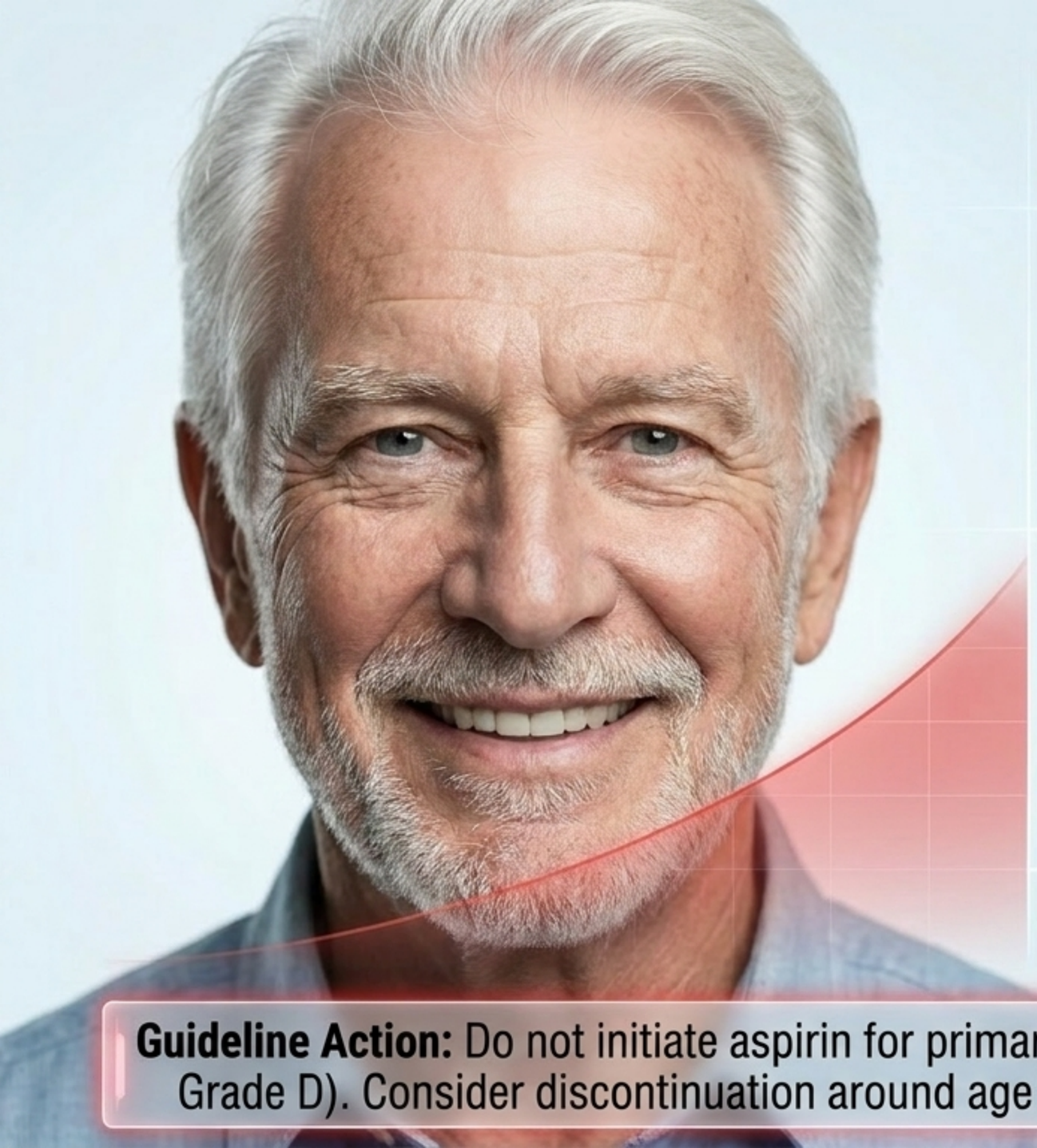
Benefit: Serious Vascular Events Reduced

8.5% vs 9.6%
Absolute Risk Reduction: ~1.1%
Number Needed to Treat (NNT): ~91

Harm: Major Bleeding Increased

4.1% vs 3.2%
Absolute Risk Increase: ~0.9%
Number Needed to Harm (NNH): ~112

Conclusion: The benefit and bleeding excess are inextricably, closely matched. No subgroup shows benefit clearly exceeding harm. Requires individualized, shared decision-making.



ASPREE Trial Cohort

19,114 community-dwelling adults, largely aged 70+.
100mg daily vs placebo.

Efficacy Failure

Cardiovascular Disease: 10.7 vs 11.3 events per 1,000 person-years (Not significant, HR 0.95).
No prolongation of disability-free survival.

Bleeding Dominance

Major Hemorrhage: 8.6 vs 6.2 events per 1,000 person-years (Significant increase, HR 1.38).

Guideline Action: Do not initiate aspirin for primary prevention in adults aged 60 or older (USPSTF Grade D). Consider discontinuation around age 75. (Does not apply to secondary prevention).

Body Weight Note

Rothwell's analysis suggests 81mg may lose efficacy at higher body weights, but ASPREE and pharmacodynamic data do not confirm this. Weight-tailored dosing remains intriguing but is not clinically actionable under current guidelines.

The Background Therapy Effect

Event rates were far lower than projected (~9% vs anticipated 17%) because participants were highly protected by concurrent statins and antihypertensives, shrinking aspirin's incremental value.

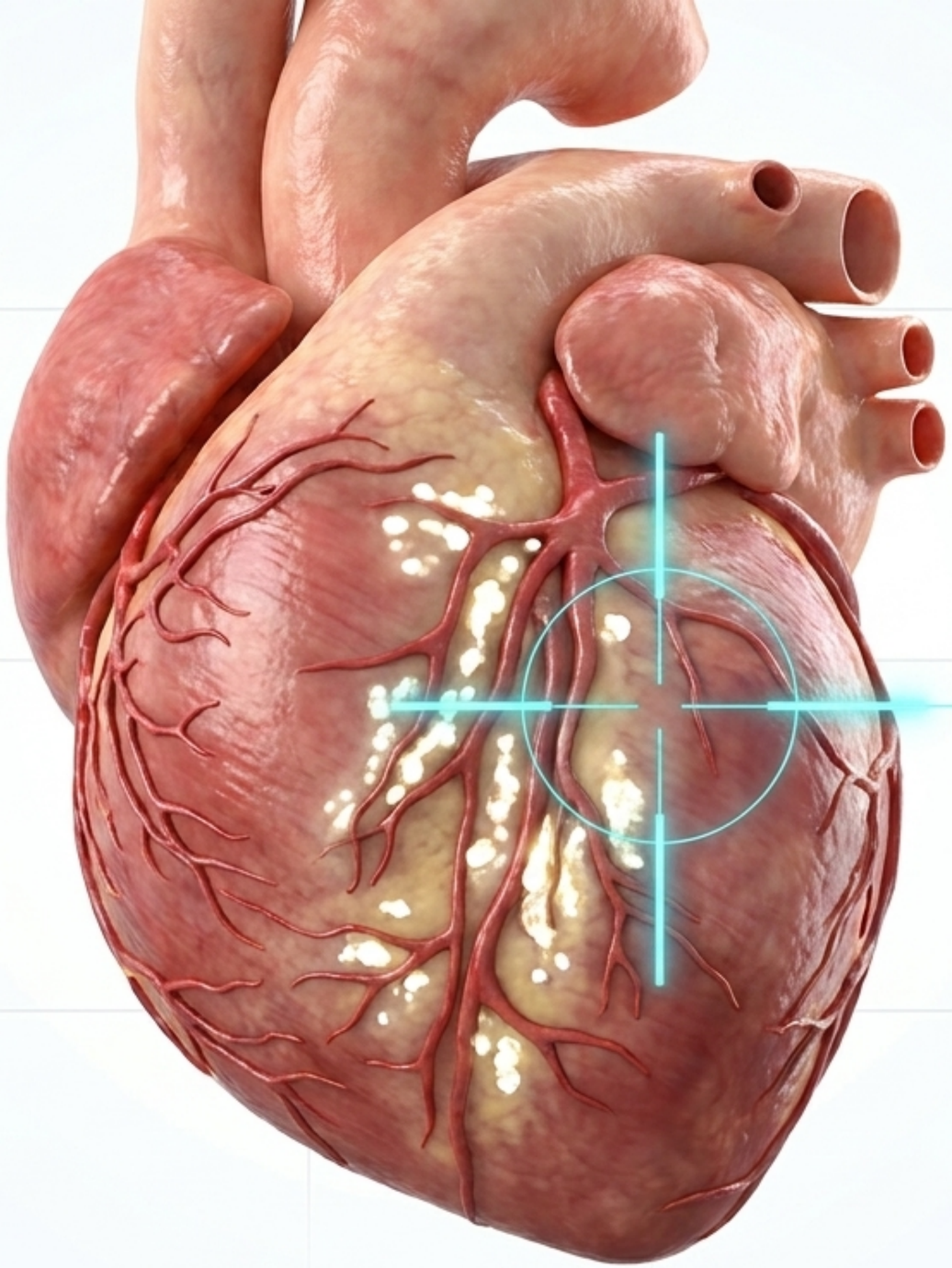
ARRIVE Trial - Moderate Risk

12,546 patients at moderate cardiovascular risk. No significant reduction in primary composite endpoints. More GI bleeding.

Concomitant Risks: Active smoking and uncontrolled hypertension raise BOTH atherosclerotic and bleeding risks. Adding aspirin does not tip the balance favorably; aggressive control of BP and tobacco is the priority.

The Precision Tool

Because population risk equations imperfectly identify beneficiaries, Coronary Artery Calcium (CAC) scoring allocates primary-prevention aspirin to those most likely to gain by identifying subclinical plaque burden.



MESA Observational Modeling

Modeled net effects for aspirin-naive adults <70 years not at high bleeding risk
(Assuming 12% relative reduction in CVD events, 42% relative increase in major bleeding).

CAC = 0 (Pristine Artery)

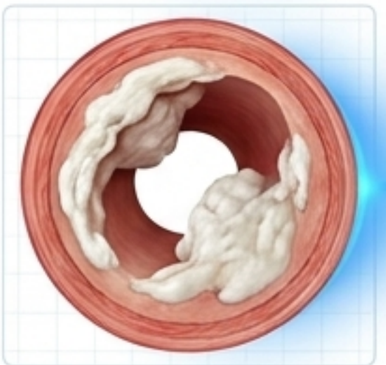
5-year NNT: 1,190.
5-year NNH: 567.

Modeled Net Effect: **Net Harm.**
Bleeding risk dominates.
Action: Avoid aspirin.

Overall Cohort (Mixed Plaque)

5-year NNT: 476.
5-year NNH: 355.

Modeled Net Effect:
Harm >= Benefit.

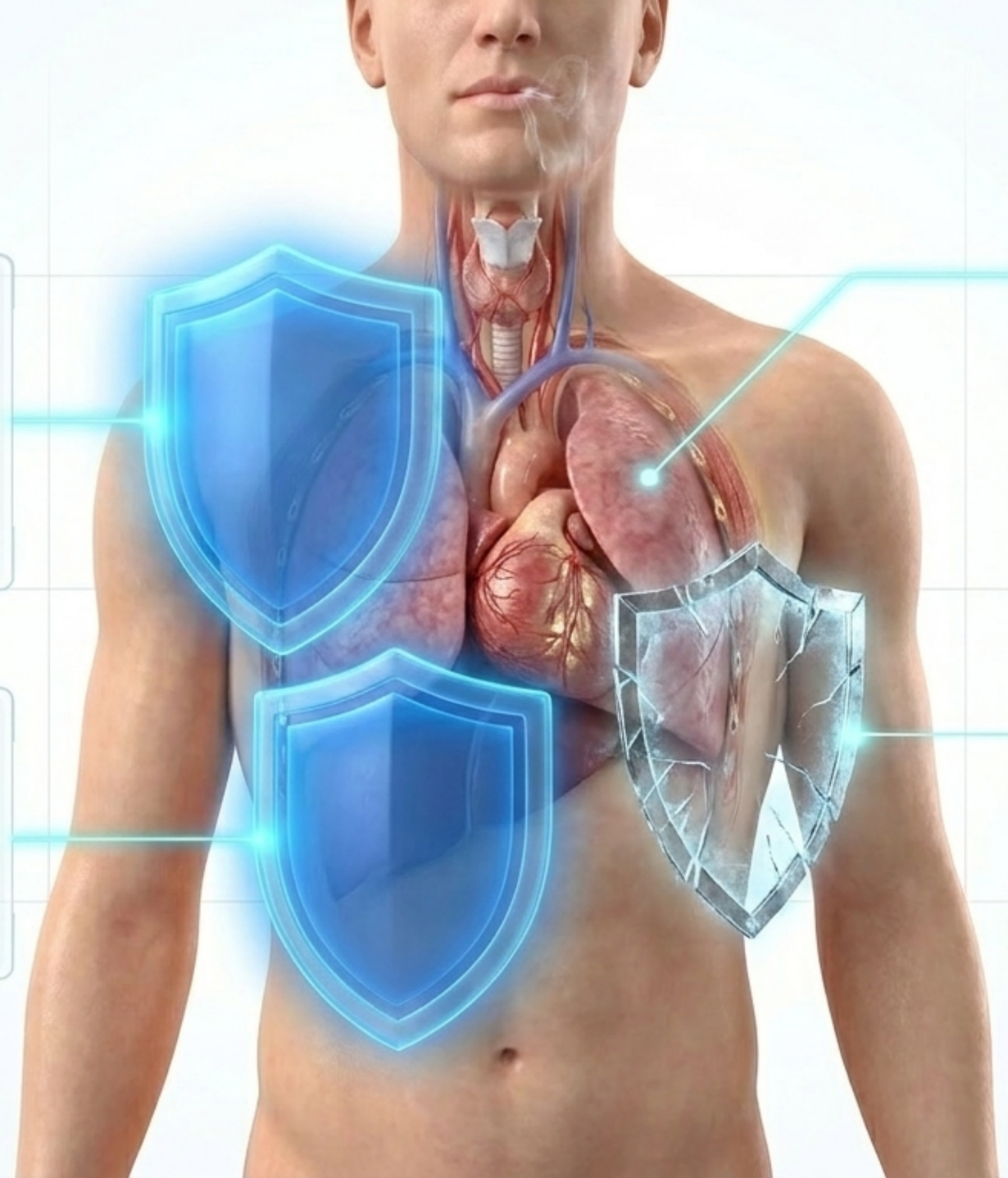


CAC >= 100 (Visible Calcified Plaque)

5-year NNT: 140.
5-year NNH: 518.

Modeled Net Effect: **Net Benefit.**
Biologically justified if bleeding risk is low.

Caveat: These are modeled inferences from observational data to inform shared decision-making, pending randomized confirmation.



Statins:

Substantially reduce major cardiovascular events without increasing major hemorrhage. Serious adverse effects are rare.

Blood Pressure Control:

Reduces stroke and MI without raising bleeding risk; directly lowers risk of hemorrhagic stroke.

Smoking Cessation:

Produces large, rapid reductions in cardiovascular risk.

The Shrinking Incremental Benefit:

As background statin use and BP control reduce residual ischemic risk, the incremental absolute benefit of adding aspirin shrinks to near zero, while its bleeding risk persists unchanged.

Scenario	Action	Rationale
Secondary Prevention (ASCVD/Post-MI/Stroke/PCI)	Continue 81mg daily.	High recurrent-event risk; absolute benefit far exceeds bleeding risk. (AHA/ACC Class 1).
Primary Prevention, Age 40-59, 10-yr risk >=10%, Low Bleed Risk	Individualize.	Small net benefit depends on personal risk. (USPSTF Grade C).
Primary Prevention, Age >=60 OR High Bleeding Risk	Do Not Initiate.	No net benefit; bleeding hazard outweighs any ischemic benefit. (USPSTF Grade D).
Primary Prevention, Diabetes, No ASCVD	Individualize.	Benefit and bleeding excess closely matched. (ASCEND).
Primary Prevention, CAC = 0	Avoid.	Modeled net harm; very low ischemic risk. (MESA Modeling).

Preferred maintenance dose when indicated: 81 mg once daily. Educational document; does not establish a clinician-patient relationship.