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Aspirin and Cardiac Prevention

Michael Blaha, MD MPH

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The Ciccarone Center

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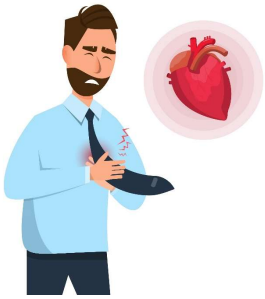

Case: Mr. Henry

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Chief compliant	A 55-year-old gentleman was referred to the Johns Hopkins Cardiometabolic Clinic for risk stratification.
Personal & Family Hx	Nonsmoker, non-diabetic with good diet and exercise habits. Family history of premature CAD (father).
Vitals	BP 139/85 mmHg, HDL 60, LDL 145.
PCE	PCE: 6.4% 10-year risk of ASCVD

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Case: Mr. Henry

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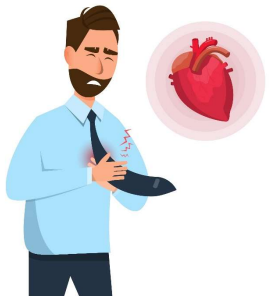

Chief compliant	A 55-year-old gentleman was referred to the Johns Hopkins Cardiometabolic Clinic for risk stratification.
Personal & Family Hx	Nonsmoker, non-diabetic with good diet and exercise habits. Family history of premature CAD (father).
Vitals	BP 139/85 mmHg, HDL 60, LDL 145.
PCE & CAC	PCE: 6.4% 10-year risk of ASCVD CAC: 325 (95th percentile) *MESA 10-year risk 12.8% with CAC (2.8% with CAC =0)*

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How Would You Treat This Patient?

A	B	C
Lifestyle therapy only	Moderate intensity statin	High intensity statin & Aspirin

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Aspirin: Currently "Under Fire"

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The rise and fall of aspirin in the primary prevention of cardiovascular disease

Inbar Raber, Cian P McCarthy, Muthiah Vaduganathan, Deepak L Bhatt, David A Wood, John G F Cleland, Roger S Blumenthal, John W McEvoy

THE LANCET

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

What do the current guidelines say?

Jacobsen A et al. Circulation. 2020;142(16);1579-1590

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2019 AHA/ACC

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]

2021 ESC Prevention Guideline

In patients with DM at high or very high CVD risk, low-dose aspirin may be considered for primary prevention in the absence of clear contraindications.[5,624,625]	IIb	A

2020 USPSTF Guideline

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.	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

Grade	Definition	Suggestions for Practice
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.	Offer or provide this service for selected patients depending on individual circumstances.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.

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Aspirin clearly overused in Primary Prevention

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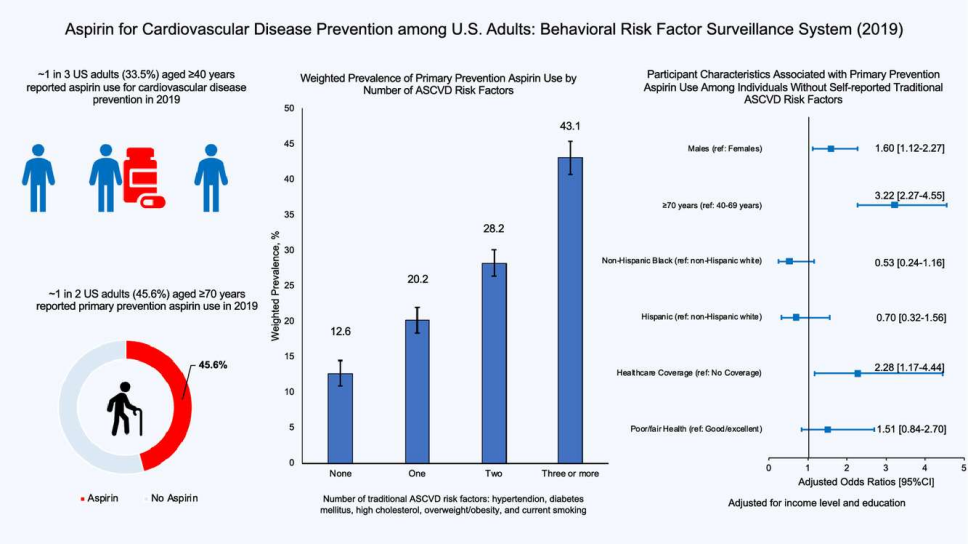

Boakye E et al. Am J Prev Cardiol. 2021 Sep 22;8:100256.

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How does Aspirin work?

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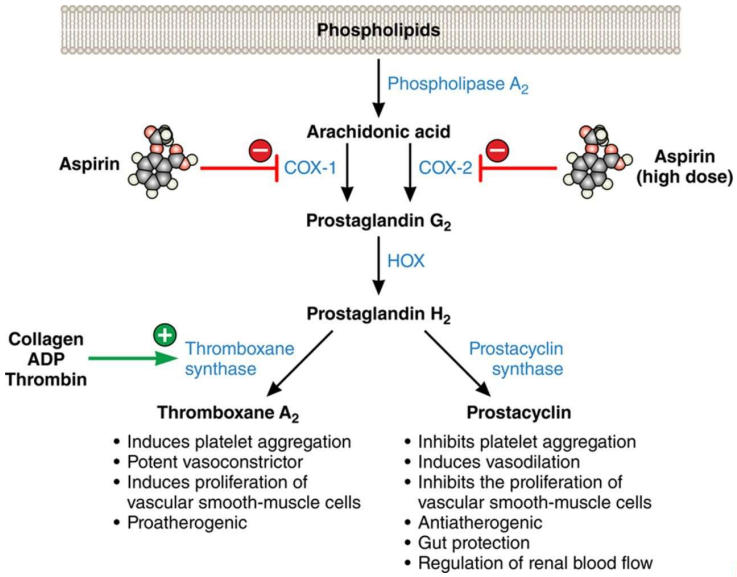

Capodanno D et al. Circulation. 2016;134:1579–1594

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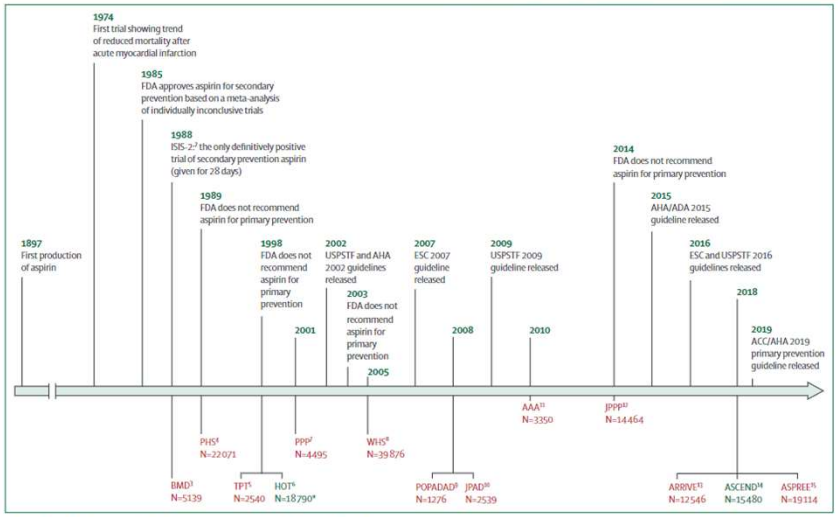

Figure: History of aspirin for use in the primary prevention of cardiovascular disease
Includes major completed trials, US FDA reviews, and international practice guidelines. Green indicates trials with significant reduction in the primary endpoint. Red indicates trials without significant reduction in the primary endpoint. AAA=aspirin for asymptomatic atherosclerosis. ADA=American Diabetes Association. AHA=American Heart Association. ARRIVE=aspirin to reduce risk of initial vascular events. ASCEND=a study of cardiovascular events in diabetes. ASPREE=aspirin in reducing events in the elderly. BMD=British male doctors. ESC=European Society of Cardiology. FDA=Food and Drug Administration. HOT=hypertension optimal treatment. ISIS-2=second international study of infarct survival. JPAD=Japanese primary prevention of atherosclerosis with aspirin for diabetes. JPPP=Japanese primary prevention project. PHS=physicians' healthy study. POPADAD=prevention of progression of arterial disease and diabetes. PPP=primary prevention project. TPT=thrombosis prevention trial (excluding warfarin arm). USPSTF=US Preventive Services Task Force. WHS=women's health study. *Ambiguity exists around the primary composite outcome in HOT[6] and the benefit for aspirin was susceptible to changes in the outcome tested.

Raber I, McEvoy JW et al. Lancet. 2019;393:2155-2167.

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Classic Trials in 1º Prevention

- **PHS (1989)**
- **TPT (1998)**
- **HOT (1998)**
- **PPP (2001)**
- **WHS (2005)**

In the primary prevention project (PPP),[7] 4495 men and women with one or more cardiovascular risk factors were randomly assigned to receive 100 mg/day aspirin or no aspirin, without masking. The trial was terminated at the second interim analysis, again despite no difference in the prespecified primary outcome, after a median follow-up of 4 years showed a 44% reduction in cardiovascular death (RR 0·56, 95% CI 0·31–0·99) and 23% reduction in total cardiovascular events (0·77, 0·62–0·95) with aspirin. No significant treatment effect was observed for all-cause mortality, and an increased rate of severe bleeding in the aspirin group (1·1% *vs* 0·3%; p=0·0008) was apparent.

Large reductions in ASCVD events, particularly Mis
Frequent early termination of trials due to evidence of **large benefit**

Raber I et al. Lancet 2019; 393: 2155-67

Three new aspirin trials in three different populations:

ARRIVE	ASCEND	ASPREE
Moderate Risk (ASCVD > 20%)	Diabetes	Age > 70
↔ MACE ↑ bleeding	↓ MACE ↑↑ bleeding	↔ MACE ↑ bleeding ↑ mortality

The Curbsiders Episode #128: Aspirin: Overhyped and Overused

THE CURB SIDERS INTERNAL MEDICINE

Aspirin in 1º Prevention Trials - JAMA 2019

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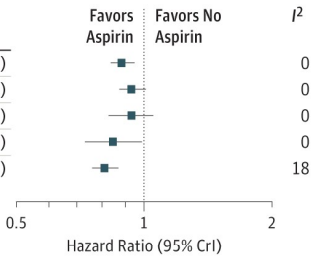
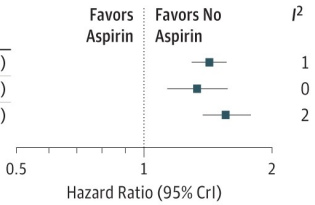
Cardiovascular Outcomes	No. of Studies	Aspirin No. of Events	Aspirin No. of Participants	No Aspirin No. of Events	No Aspirin No. of Participants	Absolute Risk Reduction, % (95% CI)	HR (95% CrI)	I^2
Composite CV outcome	13	2911	79717	3342	80057	0.41 (0.23 to 0.59)	0.89 (0.84-0.94)	0
All-cause mortality	13	3622	81623	3588	80057	0.13 (-0.07 to 0.32)	0.94 (0.88-1.01)	0
CV mortality	13	995	81623	997	80057	0.07 (-0.04 to 0.17)	0.94 (0.83-1.05)	0
Myocardial infarction	13	1469	81623	1599	80057	0.28 (0.05 to 0.47)	0.85 (0.73-0.99)	0
Ischemic stroke	10	831	65316	942	63752	0.19 (0.06 to 0.30)	0.81 (0.76-0.87)	18



Bleeding Outcomes	No. of Studies	Aspirin No. of Events	Aspirin No. of Participants	No Aspirin No. of Events	No Aspirin No. of Participants	Absolute Risk Increase, % (95% CI)	HR (95% CrI)	I^2
Major bleeding	11	1195	74715	834	73143	0.47 (0.34 to 0.62)	1.43 (1.30-1.56)	1
Intracranial bleeding	12	349	80985	257	79419	0.11 (0.04 to 0.18)	1.34 (1.14-1.57)	0
Major GI bleeding	10	593	70336	380	70465	0.30 (0.20 to 0.41)	1.56 (1.38-1.78)	2



Zheng et al. JAMA. 2019; 321(3):277-287.

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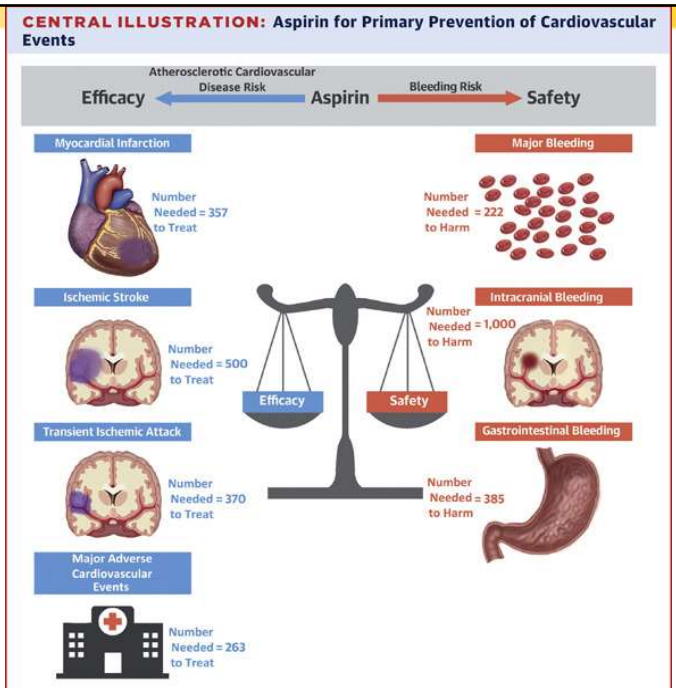

Abdelaziz, H.K. et al. J Am Coll Cardiol. 2019;73(23):2915-29.

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Aspirin Bleeding Risk Calculator

This calculator is based on sex-specific Cox proportional hazards models for predicting the 5-year risk of a first CVD event or a major bleed using a contemporary cohort of over 385,000 people without established CVD who had CVD risk assessed in New Zealand primary care. For further information about the calculator, click on More Info.

More Info

Patient Details

Sex: ✔ Male | Female

Age: 55 years old

Ethnicity: ✔ NZ European | Māori | Pacific | Indian | Chinese | Other Asian | Other

Deprivation: ✔ 1 (least) | 2 | 3 | 4 | 5 (most)

Smoking: Current | Ex-Smoker | ✔ Never

Clinical History (Select all that apply): ✔ Family Hx of CVD | Diabetes | Cancer | GI Bleed | Other Bleed | Peptic Ulcer Disease | Alcohol Related Conditions | Chronic Liver Disease | Chronic Pancreatitis

Systolic Blood Pressure: 110 mmHg

Total/HDL Cholesterol: 3 Ratio

Medication within last 6 months (Select all that apply): Lipid Lowering | Blood Pressure Lowering | PUD Drugs | NSAID | Corticosteroids | SSRI

Reset

Major Bleed in 5 years

Risk (%): No Aspirin 1% | With Aspirin 1%

Risk (per 1,000): No Aspirin 7 per 1,000 | With Aspirin 11 per 1,000

CVD Event in 5 years

Risk (%): No Aspirin 2% | With Aspirin 2%

Risk (per 1,000): No Aspirin 19 per 1,000 | With Aspirin 17 per 1,000

Effect With Aspirin

Major Bleeds Caused over 5 years: ↑ 4 per 1,000

CVD Events Avoided over 5 years: ↓ 2 per 1,000

Summary

Demographic	NZDep	Smoking	History	SBP	TCHDL	Medication
Male, 55, NZ European	1	Never Smoked	Family Hx CVD	110	3	-

© University of Auckland 2019

Selak V, et al. Ann Intern Med. 2019;171:529-539.

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Our Case: Mr. Henry

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Effect With Aspirin

Major Bleeds Caused over 5 years: ↑ 4 per 1,000

CVD Events Avoided over 5 years: ↓ 2 per 1,000

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HOW CAN WE IMPROVE ESTIMATION OF NET BENEFIT FROM ASPIRIN?

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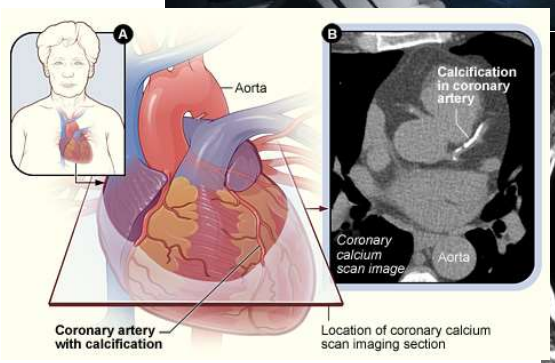
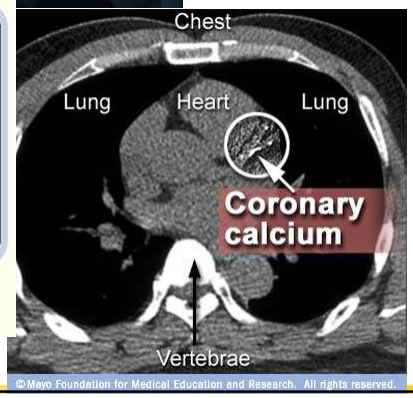
~1 mSv





Conventional view of risk factors

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Concept of negative risk factors

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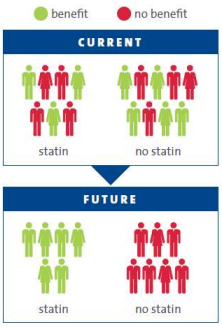
Associations between C-reactive protein, coronary artery calcium, and cardiovascular events: implications for the JUPITER population from MESA, a population-based cohort study

Michael J Blaha, Matthew J Budoff, Andrew P DeFilippis, Ron Blankstein, Juan J Rivera, Arthur Agatston, Daniel H O'Leary, Joao Lima, Roger S Blumenthal, Khurram Nasir

THE LANCET

Interpretation CAC seems to further stratify risk in patients eligible for JUPITER, and could be used to target subgroups of patients who are expected to derive the most, and the least, absolute benefit from statin treatment. Focusing of treatment on the subset of individuals with measurable atherosclerosis could allow for more appropriate allocation of resources.



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Current Guidelines – Coronary Artery Calcium

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IIa	B-NR	In intermediate-risk or selected borderline-risk adults, if the decision about statin use remains uncertain, it is reasonable to use a CAC score in the decision to withhold, postpone or initiate statin therapy.

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OUR RESEARCH

CORONARY ARTERY CALCIUM AND ASPIRIN NET BENEFIT IN THE MULTIETHNIC STUDY OF ATHEROSCLEROSIS

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Circulation

Coronary Artery Calcium for Personalized Allocation of Aspirin in Primary Prevention of Cardiovascular Disease in 2019

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MESA

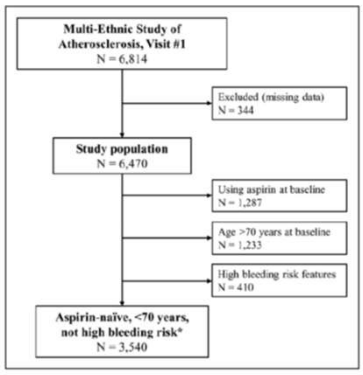

Figure 1. Flow of MESA participants included in the study.
*Participants included in the aspirin benefit/harm calculations. MESA indicates Multi-Ethnic Study of Atherosclerosis.

Table 2. Crude 5-Year Incidence Rates of Cardiovascular Disease, Coronary Heart Disease, and Major Bleeding Events

Risk		CAC Score		
	All	0	1–99	≥100
All				
Cardiovascular disease	3.52 (2.73–4.53)	1.39 (0.84–2.30)	4.58 (2.92–7.18)	12.35 (8.41–18.14)
Coronary heart disease	2.34 (1.72–3.19)	0.65 (0.31–1.36)	2.88 (1.64–5.08)	9.92 (6.47–15.22)
Major bleeding	1.34 (0.89–2.02)	0.83 (0.43–1.60)	2.89 (1.64–5.09)	0.93 (0.23–3.70)

ASPIRIN

Aspirin Net Benefit According to CAC Scores – Updated 2020 Analysis

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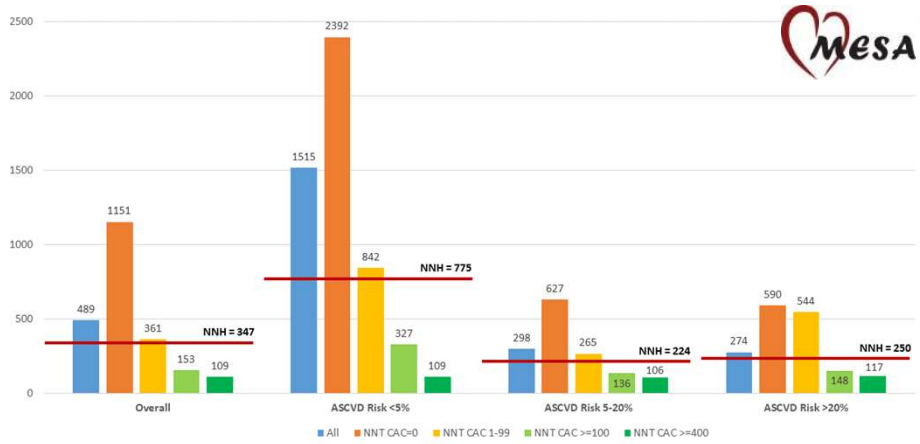
MESA



Cainzos-Achirica, et al.– *Circulation* 2020

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Clinical Perspective

What Is New?

- The value of the coronary artery calcium (CAC) score to inform the allocation of aspirin in primary prevention had not been evaluated after publication of updated 2019 meta-analysis data on the efficacy and safety of aspirin and of the 2019 American College of Cardiology/American Heart Association primary prevention guidelines.
- The pooled cohort equations and, in particular, an estimated cardiovascular risk threshold of >20% failed to identify optimal candidates for aspirin therapy.
- The CAC score was able to identify subgroups of individuals (overall and within estimated risk strata) in which aspirin would yield net benefit (CAC≥100) and in which aspirin would yield net harm (CAC=0).

What Are the Clinical Implications?

- In primary prevention individuals considered potentially good candidates for low-dose aspirin therapy (age <70 years, no high bleeding risk, believed to be at higher risk), clinicians may want to quantify the CAC score to guide personalized aspirin allocation.
- Individuals with CAC≥100 and, in particular, CAC≥400 may be good candidates for aspirin therapy for primary prevention, although the net expected benefit will likely be modest.
- In the presence of CAC=0, the risk of bleeding is greater than the potential benefit, and aspirin therapy for primary prevention should be avoided.

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CONFIRMATORY RESEARCH

CORONARY ARTERY CALCIUM AND ASPIRIN NET BENEFIT IN THE DALLAS HEART STUDY

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JAMA Cardiology | Original Investigation

Value of Coronary Artery Calcium Scanning in Association With the Net Benefit of Aspirin in Primary Prevention of Atherosclerotic Cardiovascular Disease

Ezimamaka Ajufo, BM; Colby R. Ayers, MS; Rebecca Vigen, MD, MSCS; Parag H. Joshi, MD, MHS; Anand Rohatgi, MD, MSCS; James A. de Lemos, MD; Amit Khera, MD, MSc

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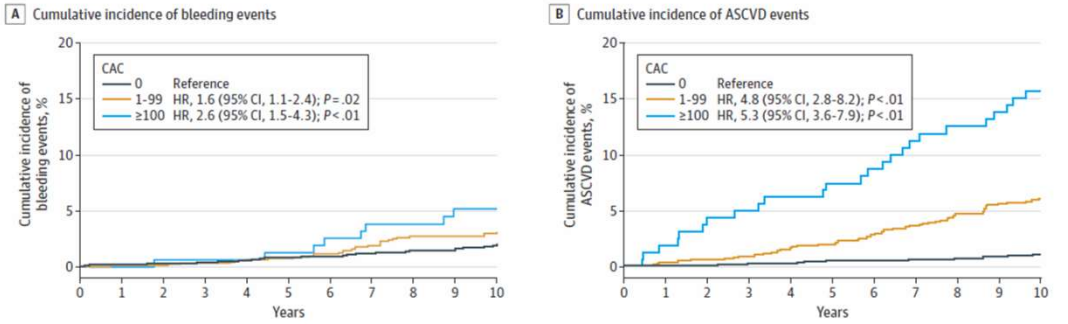
Figure 1. Cumulative Incidence of Bleeding Events and Atherosclerotic Cardiovascular Disease (ASCVD) Events Stratified by Coronary Artery Calcium (CAC)



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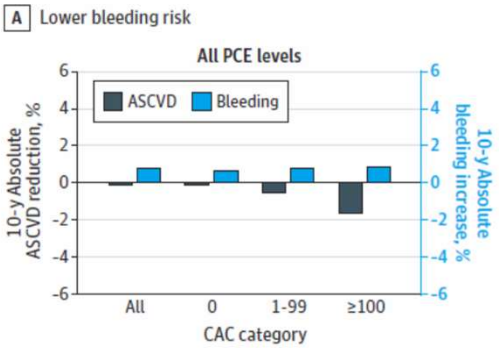

CONCLUSIONS AND RELEVANCE Higher CAC is associated with both ASCVD and bleeding events, with a stronger association with ASCVD. A high CAC score identifies individuals estimated to derive net benefit from primary prevention aspirin therapy from those who would not, but only in the setting of lower bleeding risk and estimated ASCVD risk that is not low.

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NEW NATIONAL LIPID ASSOCIATION GUIDELINES

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Coronary Artery Calcium Scoring to Guide Prevention of ASCVD

nla

An Expert Panel of the National Lipid Association reviewed the evidence related to the use of coronary artery calcium (CAC) scoring in clinical practice for adults seen for primary prevention of atherosclerotic cardiovascular disease. Recommendations for optimal use of this test in adults of across multiple domains of primary prevention are provided.

Highlights

CAC scoring strongly informs ASCVD risk discrimination and reclassification.

CAC scoring aids in ASCVD risk prediction, *regardless of race, gender or ethnicity.*

CAC scoring aids the clinician to allocate statin therapy based on ASCVD risk.

CAC Score

Add-on Rx

Very high CAC scores may inform decision-making about add-on therapies to statins.

CAC scoring aids decision-making about aspirin therapy.

When to consider the use of CAC scoring

For adults with clinical ASCVD, CAC scoring is not recommended.

- For adults 40–75 years of age, with LDL-C 70–189 mg/dL and a 10-year ASCVD of 5–19.9%, CAC scoring can be useful to decide on the need for and intensity of preventive therapies.
  - For adults with a 10-year ASCVD risk of <5%, CAC scoring is reasonable in those with a family history of premature ASCVD, to decide on the need for and intensity of preventive therapies.

Special considerations for race/ethnicity, sex, and age

- Relative ASCVD risk increases proportionally with CAC scores similarly with all races and ethnicities. For a given CAC score incidence rates of CVD and all-cause mortality are higher in Blacks and Hispanics compared to Whites and Asians.

RECOMMENDATION: *Clinicians should use CAC scoring, when indicated, for ASCVD risk assessment, regardless of the patient's race/ethnicity or gender.*

RECOMMENDATION: *In selected individuals <40 years of age with multiple major ASCVD risk factors or a family history of premature ASCVD, it is reasonable to use CAC=0 as a factor favoring intensification of lifestyle therapy and, if necessary, initiation of statin therapy.*

RECOMMENDATION: *In adults 76–80 years of age with an LDL-C of 70–189 mg/dL in whom the decision to employ statin therapy is uncertain, CAC scoring is useful in ASCVD risk reclassification.*

Definition, prognostic significance and treatment of those with a high CAC score, multivessel involvement or left main coronary calcification

- For a given CAC score, a diffuse distribution of CAC suggests higher risk than more localized CAC.
- The presence of left main coronary calcification, especially when >25% of the total score is in the left main, suggests higher risk.
- A CAC score ≥300 is associated with proportionately higher ASCVD risk than those with scores <100, a finding suggesting benefit from greater LDL-C lowering.
- A CAC score ≥1000 is associated with an annual risk similar to that of the placebo group in the FOURIER trial, a finding consistent with the potential value of very aggressive LDL-C lowering along with other ASCVD risk reduction strategies.

RECOMMENDATION: *In adults with predominant left main coronary calcification, multi-vessel coronary involvement, or a high CAC score, stress testing or invasive coronary arteriography, in the absence of clinically relevant symptoms, is not recommended.*

RECOMMENDATION: *In adults with CAC scores ≥100, initiation of statin therapy is recommended.*

RECOMMENDATION: *In adults with CAC scores ≥300, and especially in those with CAC scores ≥1000, it is reasonable to use high intensity statin therapy, and if necessary, guideline-based add-on LDL-C lowering therapies to achieve a ≥50% reduction in LDL-C, and optimally an LDL-C <70 mg/dL.*

CAC scoring in patients with severe primary hypercholesterolemia

- Limited data on CAC scoring in individuals with LDL-C ≥190 mg/dL indicate that CAC scoring may aid in both short- and intermediate-term ASCVD risk prediction.
- In individuals with severe primary hypercholesterolemia, the finding of CAC = 0 does not preclude the need for long term evidence-based LDL-C lowering therapy.

RECOMMENDATION: *In selected adults with severe primary hypercholesterolemia, in the absence of extreme LDL-C elevation, additional major ASCVD risk factors or a family history of premature ASCVD, CAC scoring may be reasonable to inform decision-making about the need for add-on therapy to maximally tolerated statins.*

CAC scoring in patients with diabetes mellitus

- In adults 40–75 years of age with type 2 diabetes age in whom the decision has been made to initiate statin therapy, it is reasonable, for those with a CAC score >100, to choose a high-intensity statin.
- In adults 30–39 years of age with long-standing diabetes (type 1 diabetes of ≥20 years duration or type 2 diabetes of ≥10 years duration) and risk factors or microangiopathy, CAC scoring may be reasonable to aid in ASCVD risk stratification and statin treatment shared decision making.

Use of CAC scoring in allocation of aspirin therapy

- In patients with CAC ≥ 100, therapy with aspirin 81 mg daily is reasonable for those who do not have bleeding-related contraindications to such therapy.

Read the National Lipid Association's complete Scientific Statement in the journal of Clinical Lipidology.

Orringer CE, Blaha MJ, Blankstein R, Budoff MJ, Goldberg RB, Gill EA, Maki KC, Mathis L, Jacobson TA. The National Lipid Association Scientific Statement on Coronary Artery Calcium Scoring to Guide Preventive Strategies for ASCVD Risk Reduction. Journal of Clinical Lipidology (2021), doi: https://doi.org/10.1016/j.jacl.2021.02.005.

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JOHNS HOPKINS MEDICINE

OTHER HOT ISSUES IN ASPIRIN FOR PRIMARY PREVENTION

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DOSE

RESEARCH SUMMARY

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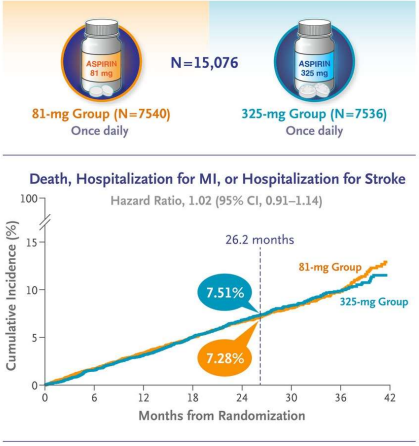
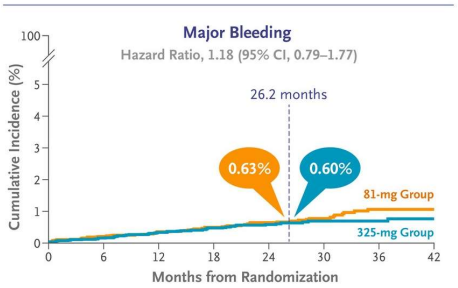
Comparative Effectiveness of Aspirin Dosing in Cardiovascular Disease

Jones WS et al. DOI: 10.1056/NEJMoa2102137





CONCLUSIONS

Effectiveness and safety outcomes did not differ significantly with daily use of 81 mg as compared with 325 mg of aspirin in patients with established atherosclerotic cardiovascular disease, and adherence was better with the 81-mg dose.

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FORMULATION

Does formulation affect adherence or GI risk?

Formulation?	There is no proven effect of different formulations of low-dose aspirin* in secondary prevention on short-, mid- or long-term patient adherence to treatment[1-6]
Formulation?	There is no proven effect of different formulations of low-dose aspirin* in secondary prevention on GI safety endpoints[1-6]
Formulation?	In some patients, there is reduced bioavailability with enteric coated aspirin

*Low dose aspirin refers to a dose of 81 mg/day or 100 mg/day.

1. Bhatt DL, et al. *Circulation* 2008;118(18):1894–1909; 2. de Abajo FJ, Garcia Rodriguez LA. *BMC Clin Pharmacol* 2001;1:1; 3. Garcia Rodriguez LA, *et al. Br J Clin Pharmacol* 2001;52(5):563–571; 4. García Rodríguez LA, *et al. PLoS One* 2016; 11(8): e0160046; 5, Derry S, Loke YK. *BMJ* 2000;321(7270):1183–1187; 6. Valkhoff VE, *et al. Can J Gastroenterol* 2013;27(3):159–167; 7. Bower A. *International Journal of Consumer Studies* 2012.1093

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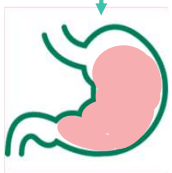
PPI USE

Bleeding risk-modifying factor: gastroprotection with a PPI

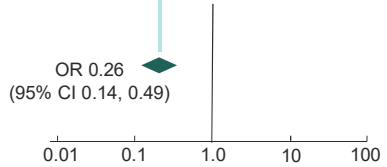
PPIs are an effective strategy for gastroprotection when using antiplatelet therapy[1–5]:

Inhibition of acid-producing proton pumps = ↓ stomach acid:
↓ the risk of GI complications



Meta-analysis of 5 RCTs in patients with high bleeding risk on low dose aspirin* with PPI vs placebo[5]

74%
lower likelihood of GI bleed with PPI treatment



In patients at high UGI bleeding risk (regardless of whether it was induced by low dose aspirin*) and under treatment with single antiplatelet therapy:

Low dose aspirin* + PPI should be considered as the first choice for UGI protection rather than clopidogrel alone and clopidogrel + PPI[6]

*Low dose aspirin refers to a dose of 100 mg/day.
CI, confidence interval; GI, gastrointestinal; OR, odds ratio; PPI, proton pump inhibitor; RCT, randomised controlled trial; UGI, upper gastrointestinal.
1. Lavie CJ, *et al. Curr Probl Cardiol* 2017;42:146–64; 2. Knuuti J, *et al. Eur Heart J* 2020;41:407–77; 3. Li L, *et al. Lancet* 2017:390:490–9; 4. Moukarbel GV, Bhatt DL. *Circulation* 2012;125:375–80;
5. Mo C, et al. *World J Gastroenterol* 2015;21:5382–92; 6. Wu W, *et al. Exp Ther Med* 2020;19:3595–603.

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BLEEDING RISK ASSESSMENT

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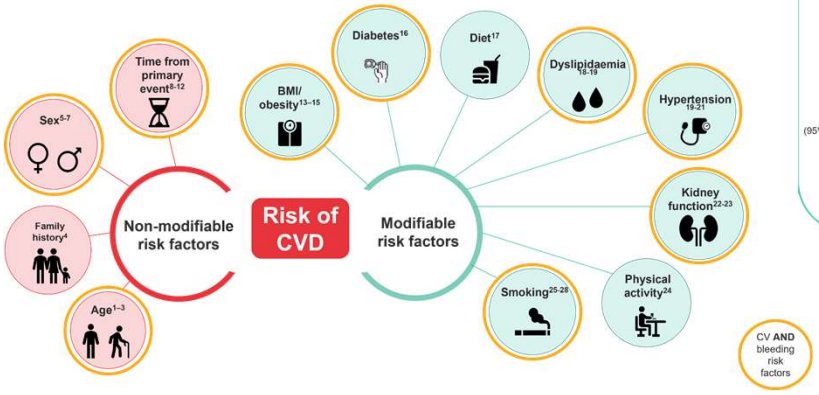
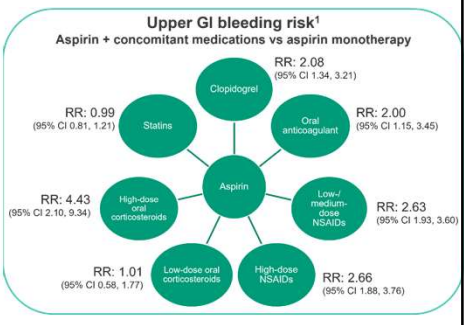
Personalized bleeding risk assessment?





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Mr. Henry

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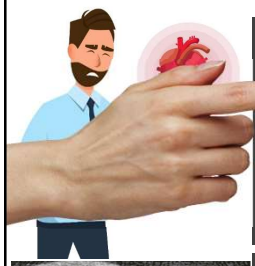
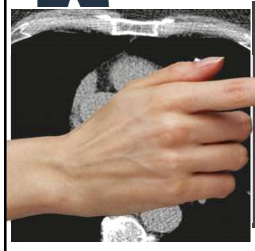


Red flags

Family Hx of premature CAD, extensive CAC

PMHx

Stage I Hypertension



Notable Lab

Moderately elevated LDL

Treatment

1. High intensity statin
2. ASA – 81mg chew, +/- PPI

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Summary

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1. Based on the data of three landmark primary prevention trials of ASA, updated guidelines are highly cautious with recommending ASA for primary prevention
2. Aspirin still "works" – however, it remains unclear how clinicians should best identify patients likely to derive net benefit from aspirin therapy in routine primary prevention
3. Carefully balancing act – bleeding risk factors must be assessed!
4. Coronary artery calcium (CAC) can simplify the identification of patients who may benefit from low dose aspirin for primary prevention, notably CAC≥100
5. In appropriate patients, consider chewable aspirin 81mg & a gastroprotective strategy to reduce bleeding adverse events & thereby improve adherence.

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QUESTIONS

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thank you!

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