Antiplatelet Therapy Update 2019:
Separating fact from #fakenews

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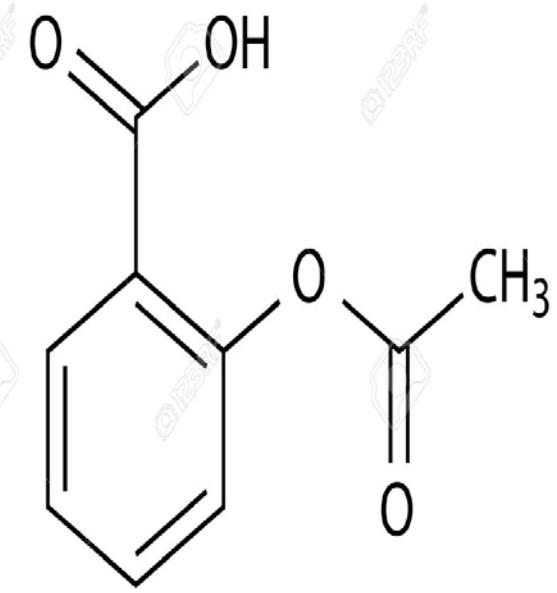
Director, Structural Heart

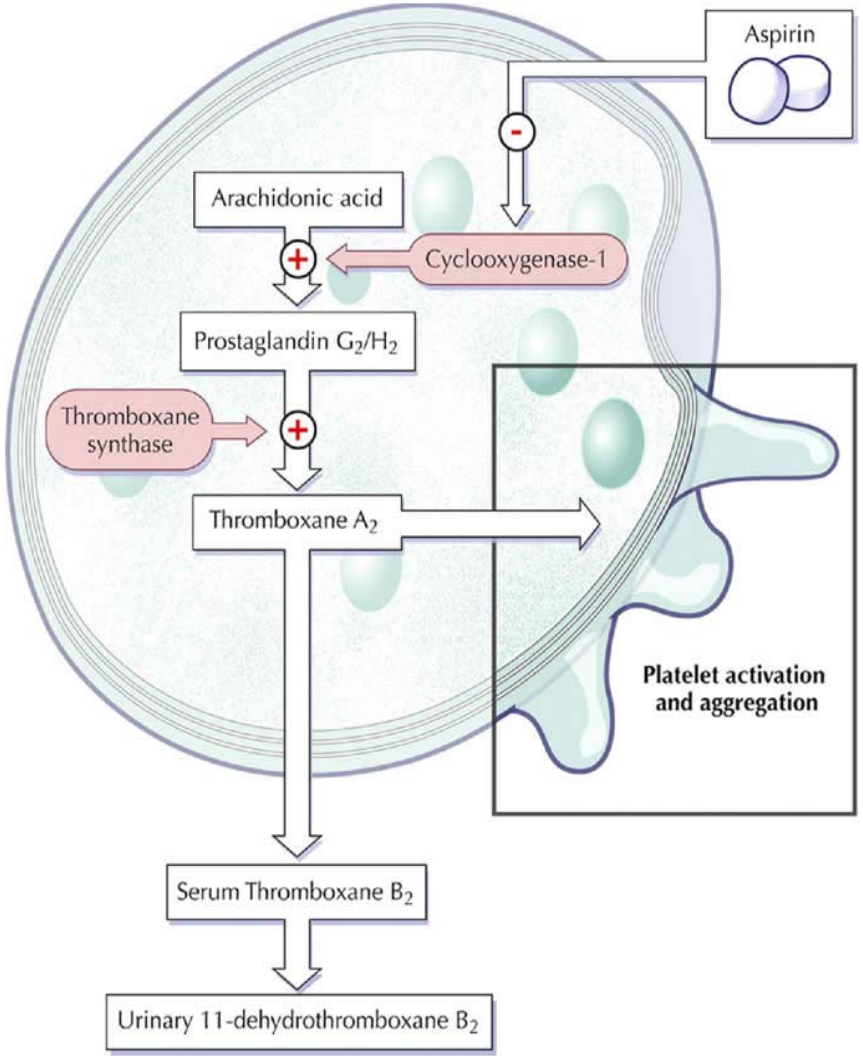
ORLANDO HEALTH®

October 5, 2019

Aspirin



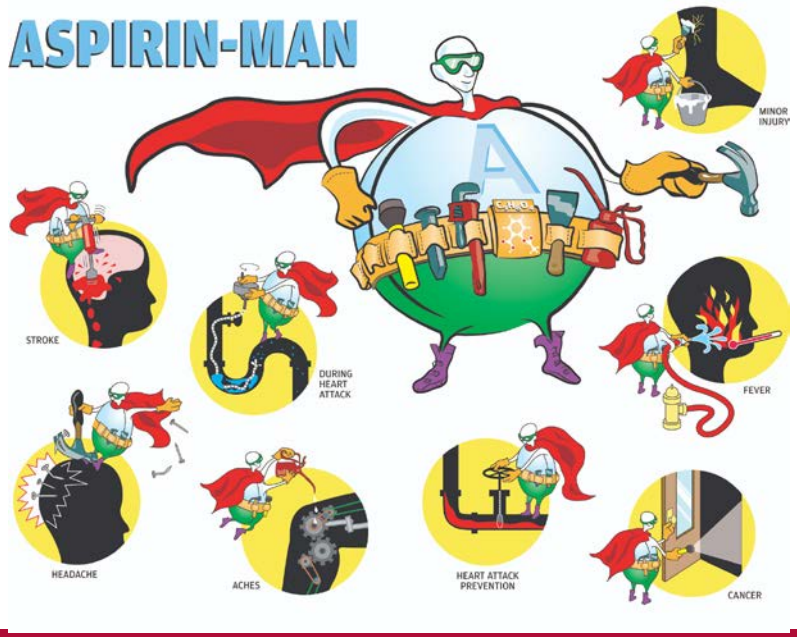
Acetylsalicylic acid



Wonder Drug?


GENUINE ASPIRIN
BAYER
BAYER
ASPIRIN (NSAID) PAIN RELIEVER/FEVER REDUCER
THE WONDER DRUG
325 mg
Safe Pain Relief Plus
Lifesaving Benefits
COATED TABLETS


BAYER
One Real Aspirin
Counterfeits and substitutes may be ineffective in preventing pregnancy. Protect yourself by demanding
Bayer-Tablets of Aspirin
Every tablet and every package of genuine Aspirin bears
"The Bayer Cross"
Your Guarantee of Moral Purity"


ASPIRIN-MAN
STROKE
DURING HEART ATTACK
MINOR INJURY
FEVER
HEADACHE
ACHES
HEART ATTACK PREVENTION
CANCER


MUM HAILS 'MIRACLE' PILL
I had baby after five miscarriages thanks to ASPIRIN
Wonder drug can reduce heart risk
Breakthrough
Precaution
myView

First Major Primary Prevention Trial

Physician's Health Study (PHS)

22,071 male participants randomized to aspirin (325 mg every other day) followed for an average of 5 years

End point	Relative Risk (95% CI)	P value
CV Mortality	0.96 (0.60-1.54)	0.87
Myocardial infarction		
Fatal	0.34 (0.15-0.75)	0.007
Nonfatal	0.59 (0.47-0.74)	<0.00001
Total	0.56 (0.45-0.70)	<0.00001
Stroke		
Fatal	1.51 (0.54-4.28)	0.43
Nonfatal	1.20 (0.91-1.59)	0.20
Total	1.22 (0.93-1.60)	0.15

Aspirin reduces the risk of myocardial Infarction among men

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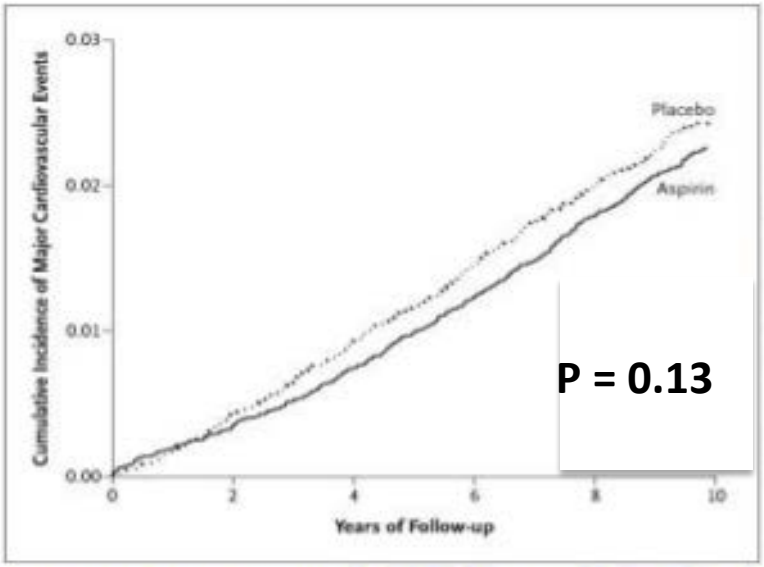
CI=Confidence interval, CV=Cardiovascular

Source: Steering Committee of the Physicians' Health Study Research Group. *NEJM* 1989;321:129-135

Aspirin in Primary Prevention

Womens' Health Study (WHS)

39,876 women randomized to aspirin (100 mg every other day) or placebo for an average of 10 years



Aspirin does not reduce cardiovascular events among women

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Source: Ridker P et al. *NEJM* 2005;352:1293-1304

Important Recent Primary Prevention Trials from 2018

- ASPREE Trial (NEJM 2018) 19,114 patients 70 years and older
  - 12.7 events per 1000 person-years ASA
  - 11.1 events per 1000 person-years on placebo
  - HR 1.14, 95% CI 1.01-1.29 (***higher risk of death with ASA)***

- ARRIVE Trial (Lancet 2018) 12,546 patients with moderate CVD risk
  - ***ASA no benefit on mortality***
  - 2.55 vs 2.57%, p = NS at 5 year follow-up

ASPREE Trial

Table 1. Mortality According to the Underlying Cause of Death.*

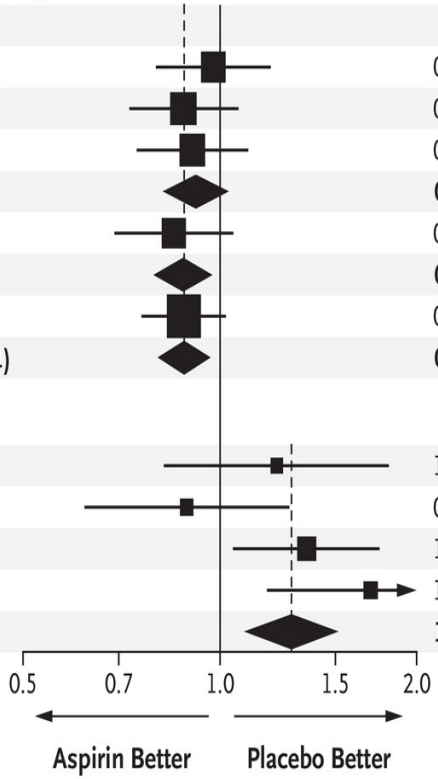
Cause of Death	Overall (N = 19,114)	Aspirin (N = 9525)	Placebo (N = 9589)	Hazard Ratio (95% CI)
	no. of deaths	*no. of deaths (%)*		
Any	1052	558 (5.9)	494 (5.2)	1.14 (1.01–1.29)
Cancer†	522	295 (3.1)	227 (2.3)	1.31 (1.10–1.56)
Cardiovascular disease, including ischemic stroke‡	203	91 (1.0)	112 (1.2)	0.82 (0.62–1.08)
Major hemorrhage, including hemorrhagic stroke§	53	28 (0.3)	25 (0.3)	1.13 (0.66–1.94)
Other¶	262	140 (1.5)	122 (1.3)	1.16 (0.91–1.48)
Insufficient information‖	12	4 (<0.1)	8 (0.1)	—

* The confidence intervals shown in this table have not been adjusted for multiple comparisons, and inferences drawn from them may not be reproducible.
† Data are shown for deaths that were related to primary or metastatic cancer.
‡ Cardiovascular disease was defined as any ischemic event (myocardial infarction, other coronary heart disease, sudden cardiac death, or ischemic stroke).
§ Major hemorrhage was defined as any hemorrhagic event (hemorrhagic stroke, symptomatic intracranial bleeding, or major gastrointestinal bleeding or other extracranial bleeding).[2]
¶ Data are shown for deaths that were related to causes that are not represented in the other categories (e.g., sepsis, chronic lung disease, dementia, or heart failure), except for deaths for which insufficient information was available to adjudicate an underlying cause.
‖ Data are shown for deaths for which insufficient information was available to adjudicate an underlying cause, even after linkage with the National Death Index. The hazard ratio was not determined because of the low numbers of deaths.

ASCEND Trial
15,480 pts with type 2DM

- ***ASA no benefit on mortality*** 9.7% vs. 10.2% p=NS; 7.4 year follow-up

Type of Event	Aspirin (N=7740)	Placebo (N=7740)	Rate Ratio (95% CI)	P Value
	no. of participants with event (%)			
Vascular Outcomes				
Nonfatal myocardial infarction	191 (2.5)	195 (2.5)	0.98 (0.80–1.19)	
Nonfatal presumed ischemic stroke	202 (2.6)	229 (3.0)	0.88 (0.73–1.06)	
Vascular death excluding intracranial hemorrhage	197 (2.5)	217 (2.8)	0.91 (0.75–1.10)	
Any serious vascular event excluding TIA	**542 (7.0)**	**587 (7.6)**	**0.92 (0.82–1.03)**	
TIA	168 (2.2)	197 (2.5)	0.85 (0.69–1.04)	
Any serious vascular event including TIA	**658 (8.5)**	**743 (9.6)**	**0.88 (0.79–0.97)**	**0.01**
Any arterial revascularization	340 (4.4)	384 (5.0)	0.88 (0.76–1.02)	
Any serious vascular event or revascularization	**833 (10.8)**	**936 (12.1)**	**0.88 (0.80–0.97)**	
Major Bleeding				
Intracranial hemorrhage	55 (0.7)	45 (0.6)	1.22 (0.82–1.81)	
Sight-threatening bleeding in eye	57 (0.7)	64 (0.8)	0.89 (0.62–1.27)	
Serious gastrointestinal bleeding	137 (1.8)	101 (1.3)	1.36 (1.05–1.75)	
Other major bleeding	74 (1.0)	43 (0.6)	1.70 (1.18–2.44)	
Any major bleeding	**314 (4.1)**	**245 (3.2)**	**1.29 (1.09–1.52)**	**0.003**



NEJM 2018

HEALTH NEWS

Millions should stop taking aspirin every day to prevent heart attacks, study says – USA TODAY

By admin Posted on July 23, 2019 5 min read 35 0

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A Woman May Have Gotten 'Broken Heart Syndrome' After Eating Too Much Wasabi at a Wedding – Gizmodo

admin 3 hours ago

One woman's wedding wasabi—apparently mistaken for avocado—ended up sending her to the emergency room ...

Prehistoric Babies Drank Animal Milk From Bottles : The Salt – NPR

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Enlarge this image A selection of small feeding vessels dating back to the late ...

Death toll climbs from vaping illnesses as Georgia reports 10th fatality in US – CNBC

EXPLORE People

Healthy Adults No Longer Need to Take Daily Aspirin to Prevent Heart Attacks

Researchers found that the risk of gastrointestinal bleeding was not worth the heart benefits

By Julie Mazziotta | March 18, 2019 06:02 PM

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PHOTO: GETTY

Healthy adults over age 70 should stop taking a daily, low dose of aspirin to

What's the Role of ASA in Primary Prevention of CVD?

- The 2019 ACC/AHA guidelines recommend low dose ASA (75 – 100mg/day) in ***primary prevention*** in which of the following circumstances.

A. In all adults over the age of 70
B. In all adults over the age of 50.
C. In adults ages 40-70 at higher risk of CVD but not at increased risk of bleeding.
D. In patients with an elevated CRP.
E. Not indicated in primary prevention.

What's the Role of ASA in Primary Prevention?

- The 2019 ACC/AHA guidelines recommend low dose ASA (75 – 100mg/day) in ***primary prevention*** in which of the following circumstances.

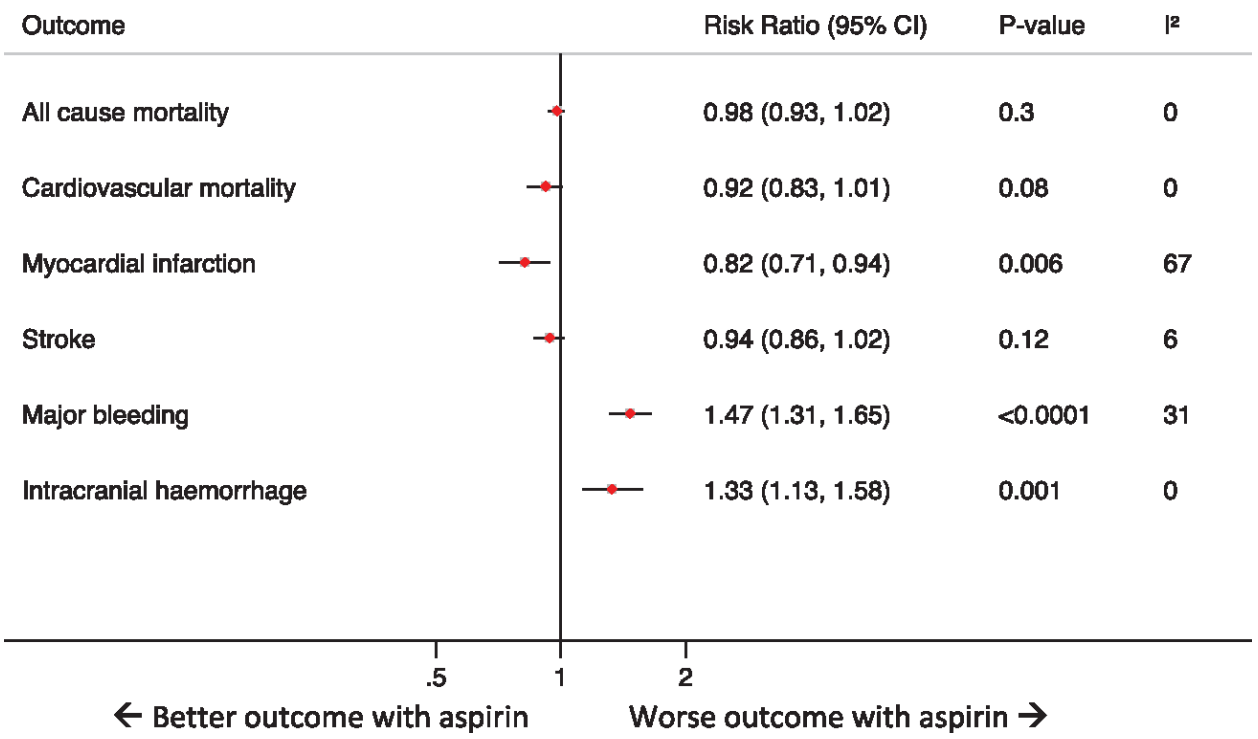
A. In all adults over the age of 70
B. In all adults over the age of 50.
C. Primary prevention in adults ages 40-70 at higher risk of CVD but not at increased risk of bleeding.
D. In patients with an elevated CRP.
E. Not indicated in primary prevention.

Society Guideline Recommendations: ASA and Primary Prevention

- 2016 US Preventive Task Force(USPSTF)
  - Low dose ASA is recommended for individuals 50 -59 who have a 10% or greater 10-year CVD risk and not at increased risk of bleeding, and have life expectancy of 10 years, and are willing to take ASA for 10 years.
- 2012 European Society of Cardiology
  - ASA not indicated in primary prevention

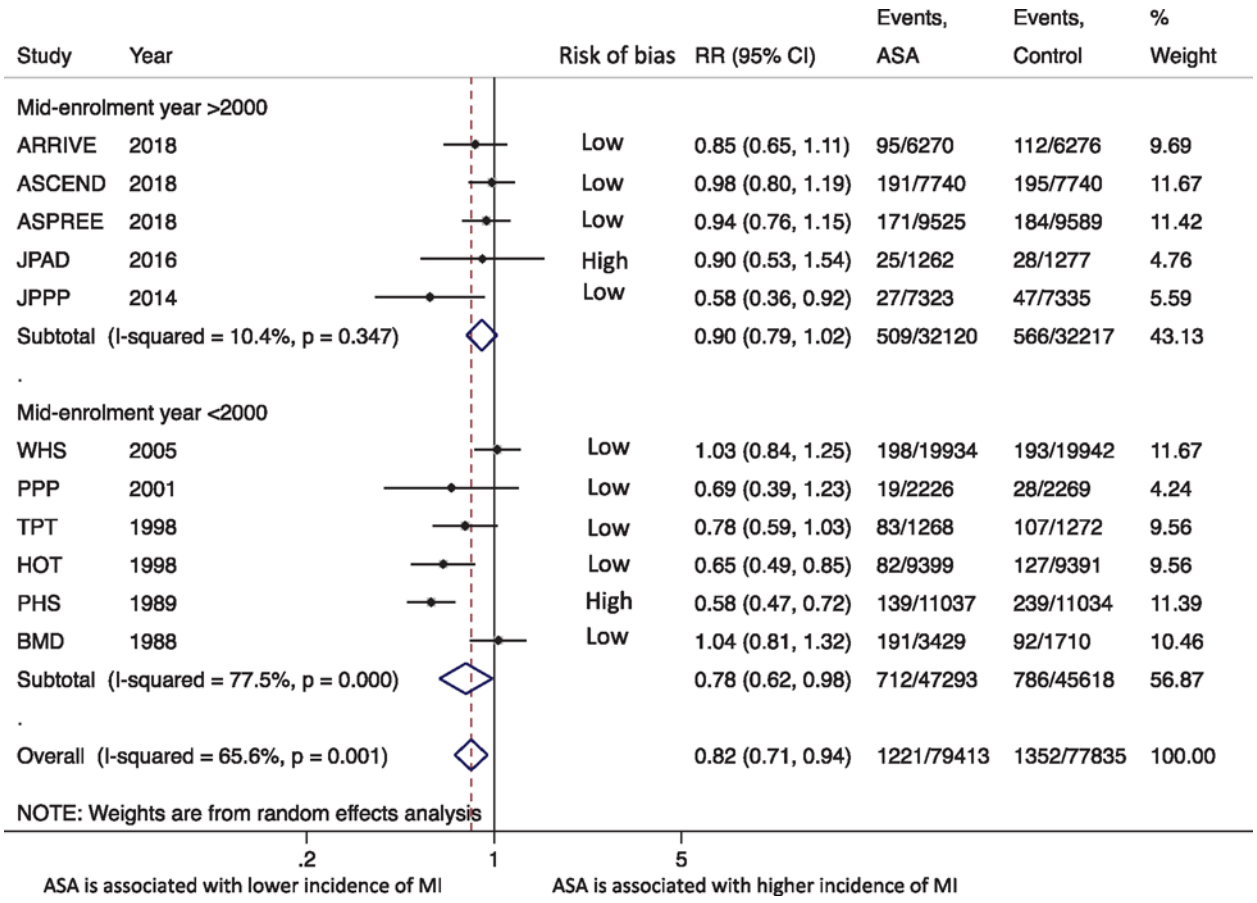
Primary Prevention ASA Meta-Analysis

11 studies 157,248 patients



European Heart Journal, Volume 40, Issue 7, 14 February 2019, Pages 607–617, https://doi.org/10.1093/eurheartj/ehy813

MI risk reduction relegated to older trials of ASA use...



European Heart Journal, Volume 40, Issue 7, 14 February 2019, Pages 607–617, https://doi.org/10.1093/eurheartj/ehy813

How many Americans over the age of 40 take ASA for primary prevention?

- A. 5 million
- B. 10 million
- C. 20 million
- D. 30 million

How many Americans over the age of 40 take ASA for primary prevention?

- A. 5 million
- B. 10 million
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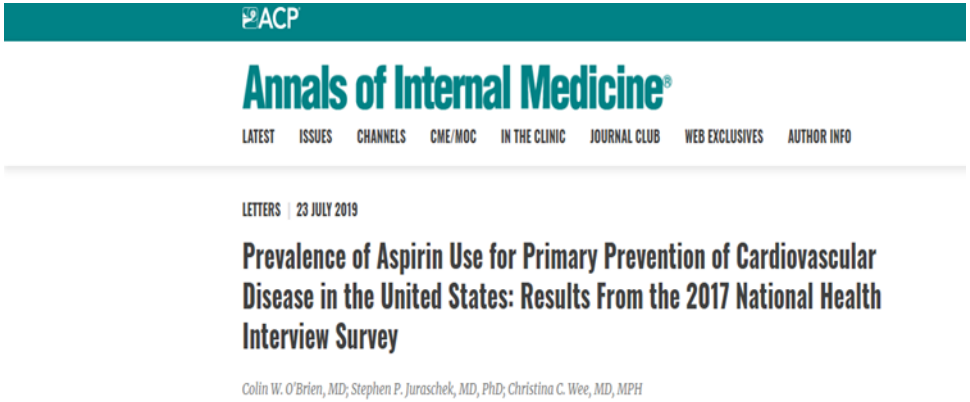
- ***D. 30 million***



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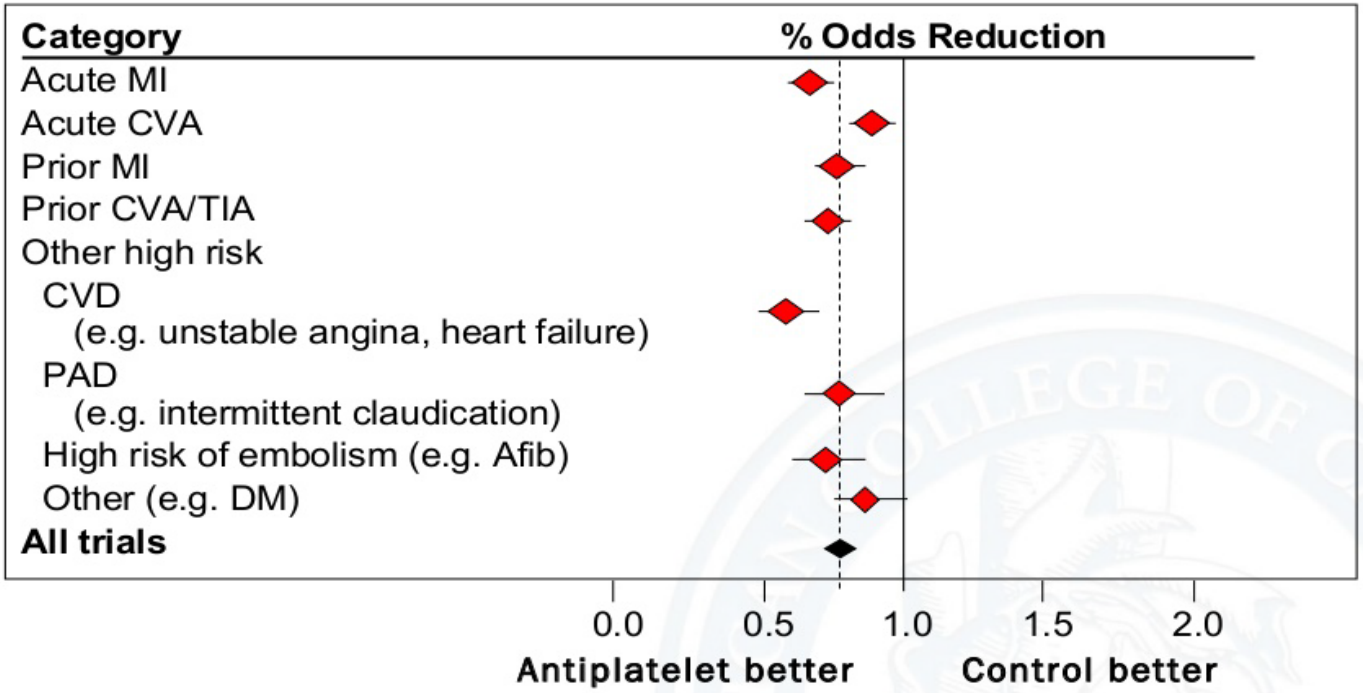
LETTERS | 23 JULY 2019

Prevalence of Aspirin Use for Primary Prevention of Cardiovascular Disease in the United States: Results From the 2017 National Health Interview Survey

Colin W. O'Brien, MD; Stephen P. Juraschek, MD, PhD; Christina C. Wee, MD, MPH

Aspirin: Secondary Prevention

Effect of antiplatelet treatment* on vascular events**



Aspirin reduces the risk of adverse cardiovascular events

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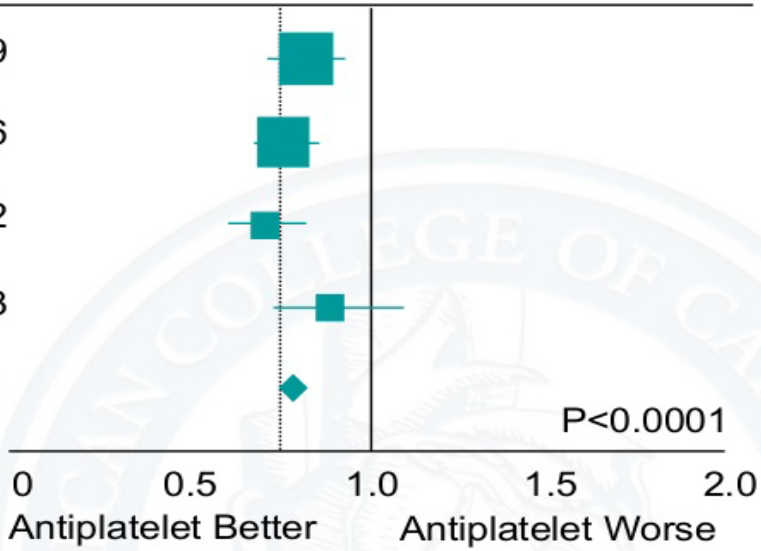
*Aspirin was the predominant antiplatelet agent studied
**Include MI, stroke, or death

Source: Antithrombotic Trialists' Collaboration. *BMJ* 2002;324:71–86

Does Aspirin dose matter?

Effect of aspirin doses on vascular events in high-risk patients (excluding those with acute stroke)

Aspirin Dose	No. of Trials	% Odds Reduction
500-1500 mg	34	19
160-325 mg	19	26
75-150 mg	12	32
<75 mg	3	13
Any aspirin	65	23



High dose aspirin does not provide improved efficacy

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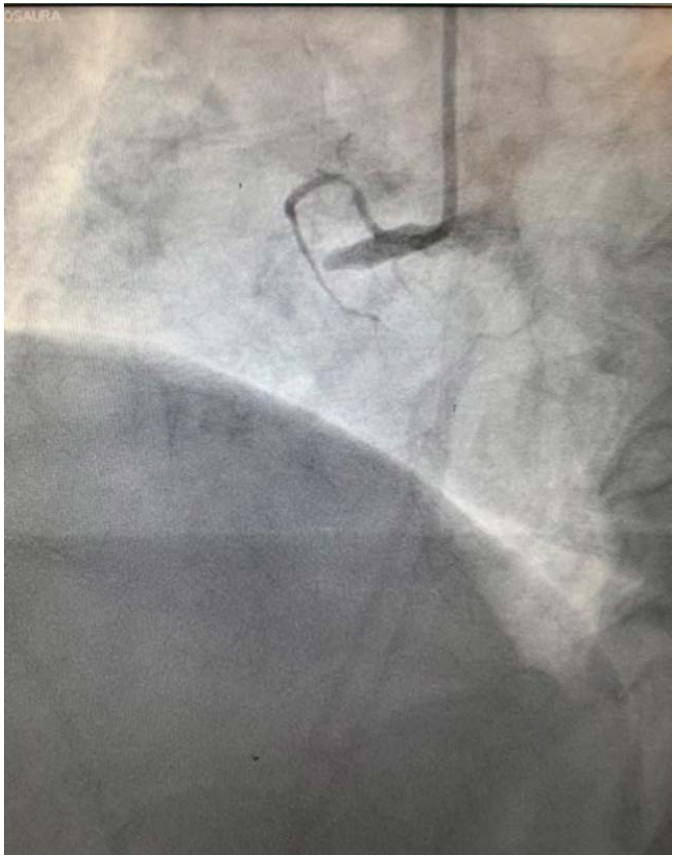
Source: Antithrombotic Trialists' Collaboration. *BMJ* 2002;324:71-86

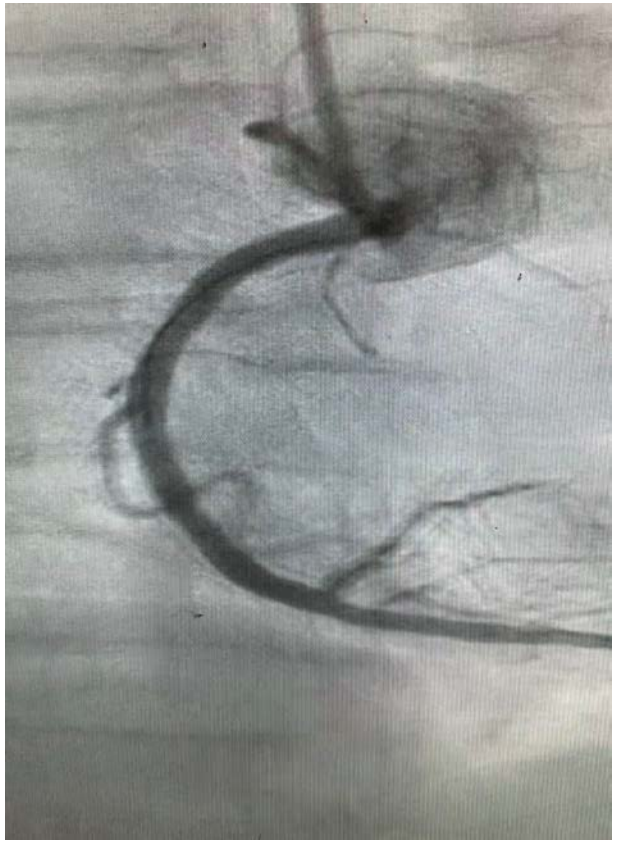
Clear Benefit of ASA in secondary prevention

- 74 year old diabetic male with equivocal stress test -- cath 3 years ago showed moderate RCA stenosis

- He was maintained on aspirin. Pre-op stress nuclear was normal
- Spine surgeon wanted him off ASA for minimum of 10 days prior to lumbar fusion.
- ASA was stopped. 2 days prior to surgery….

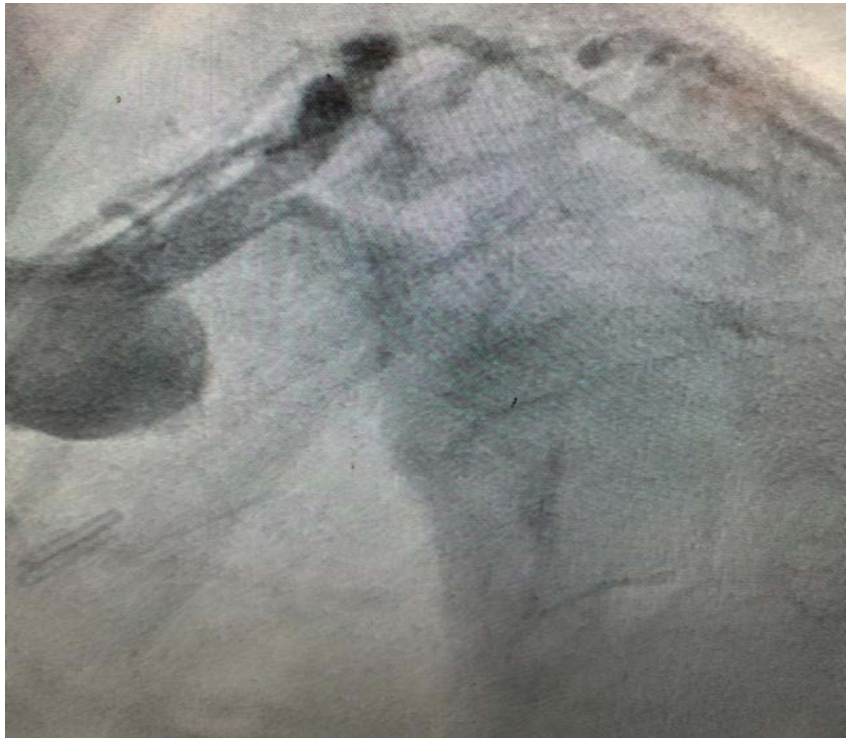
The 2am STEMI wake up call…

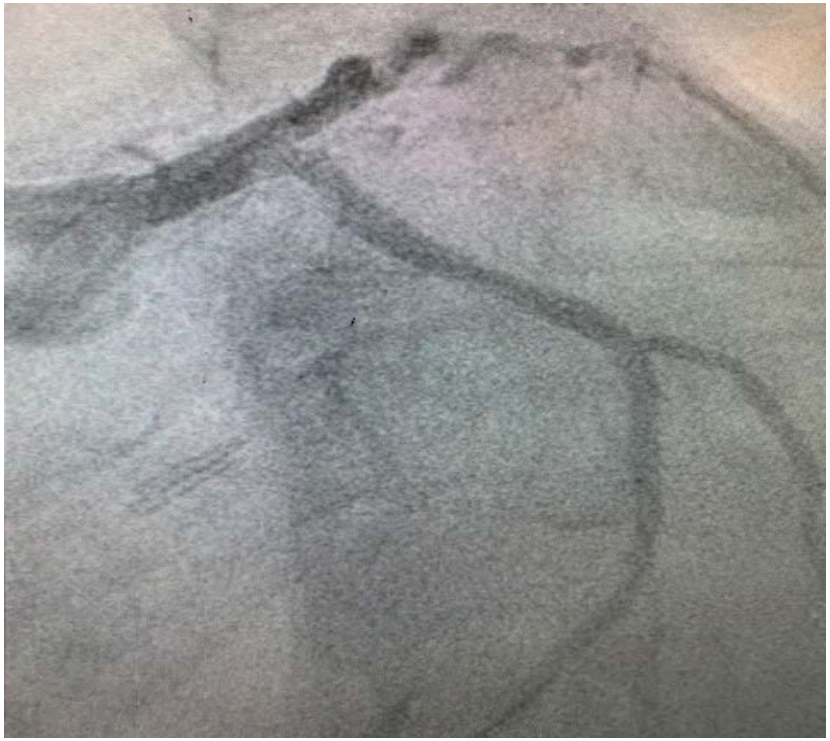




Case Scenario

- 77 year old diabetic male arrives with NSTEMI. LCX is treated with drug-eluting stent.





- **Pt has history of AFIB. CHADS VASC score of 3. What is the optimal *discharge* anticoagulant regimen for this patient with normal renal function and weight 80kg?**

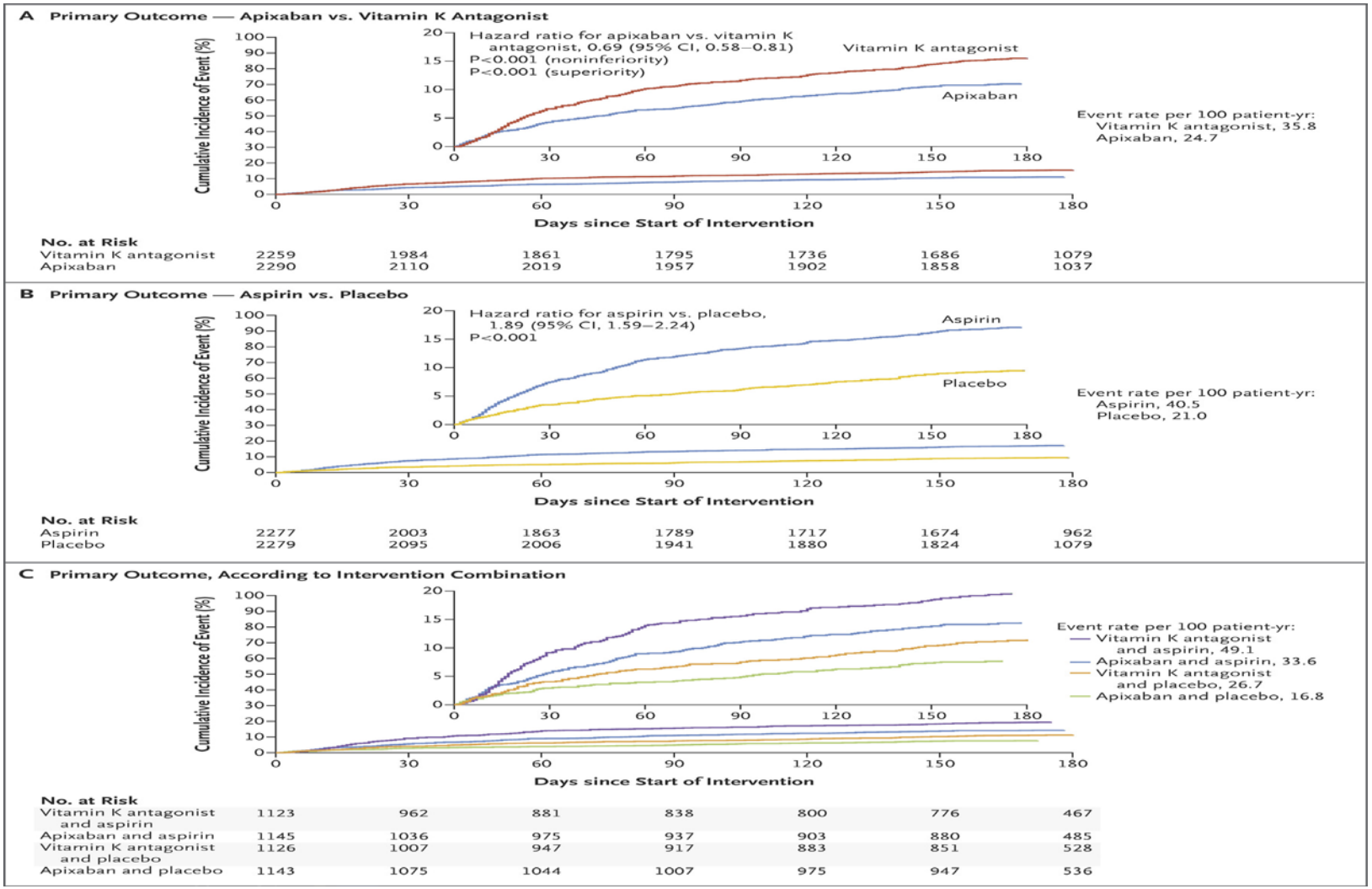
- A. ASA 81mg + Plavix 75mg + Coumadin (INR 2-3)
- B. ASA 81mg + Plavix 75mg
- C. ASA 81mg + Plavix 75mg + Eliquis 2.5mg BID
- D. Plavix 75mg + Eliquis 5mg BID

- A. ASA 81mg + Plavix 75mg + Coumadin (INR 2-3)
- B. ASA 81mg + Plavix 75mg
- C. ASA 81mg + Plavix 75mg + Eliquis 2.5mg BID
- **D. Plavix 75mg + Eliquis 5mg BID**

Augustus Trial NEJM 2018 (N=4614)

- Evaluate optimal antiplatelet regimen in patients with AFIB undergoing PCI or presenting with ACS.
- Is dual therapy better than triple therapy?
- Bleeding risks?
- All patients to have received clopidogrel.
- Randomized to 4 groups of patients
  - ASA + Plavix + Eliquis 5mg BID
  - ASA + Plavix + Coumadin
  - Plavix + Coumadin
  - Plavix + Eliquis 5mg BID

Augustus Trial



Augustus Trial

Table 2. Primary Safety and Secondary Efficacy Outcomes.*

Outcome	Apixaban	Vitamin K Antagonist	Hazard Ratio (95% CI)	P Value for Superiority
Anticoagulation-regimen comparison				
ISTH major or clinically relevant nonmajor bleeding†				
No. of patients with event/total no. (%)	241/2290 (10.5)	332/2259 (14.7)	—	—
Event rate per 100 patient-yr	24.7	35.8	0.69 (0.58–0.81)	<0.001
Death or hospitalization				
No. of patients with event/total no. (%)	541/2306 (23.5)	632/2308 (27.4)	—	—
Event rate per 100 patient-yr	57.2	69.2	0.83 (0.74–0.93)	0.002
Death or ischemic event‡				
No. of patients with event/total no. (%)	154/2306 (6.7)	163/2308 (7.1)	—	—
Event rate per 100 patient-yr	14.3	15.3	0.93 (0.75–1.16)	NS
Antiplatelet-regimen comparison	**Aspirin**	**Placebo**		
ISTH major or clinically relevant nonmajor bleeding				
No. of patients with event/total no. (%)	367/2277 (16.1)	204/2279 (9.0)	—	—
Event rate per 100 patient-yr	40.5	21.0	1.89 (1.59–2.24)	<0.001
Death or hospitalization§				
No. of patients with event/total no. (%)	604/2307 (26.2)	569/2307 (24.7)	—	—
Event rate per 100 patient-yr	65.7	60.6	1.08 (0.96–1.21)	NS
Death or ischemic event				
No. of patients with event/total no. (%)	149/2307 (6.5)	168/2307 (7.3)	—	—
Event rate per 100 patient-yr	13.9	15.7	0.89 (0.71–1.11)	NT

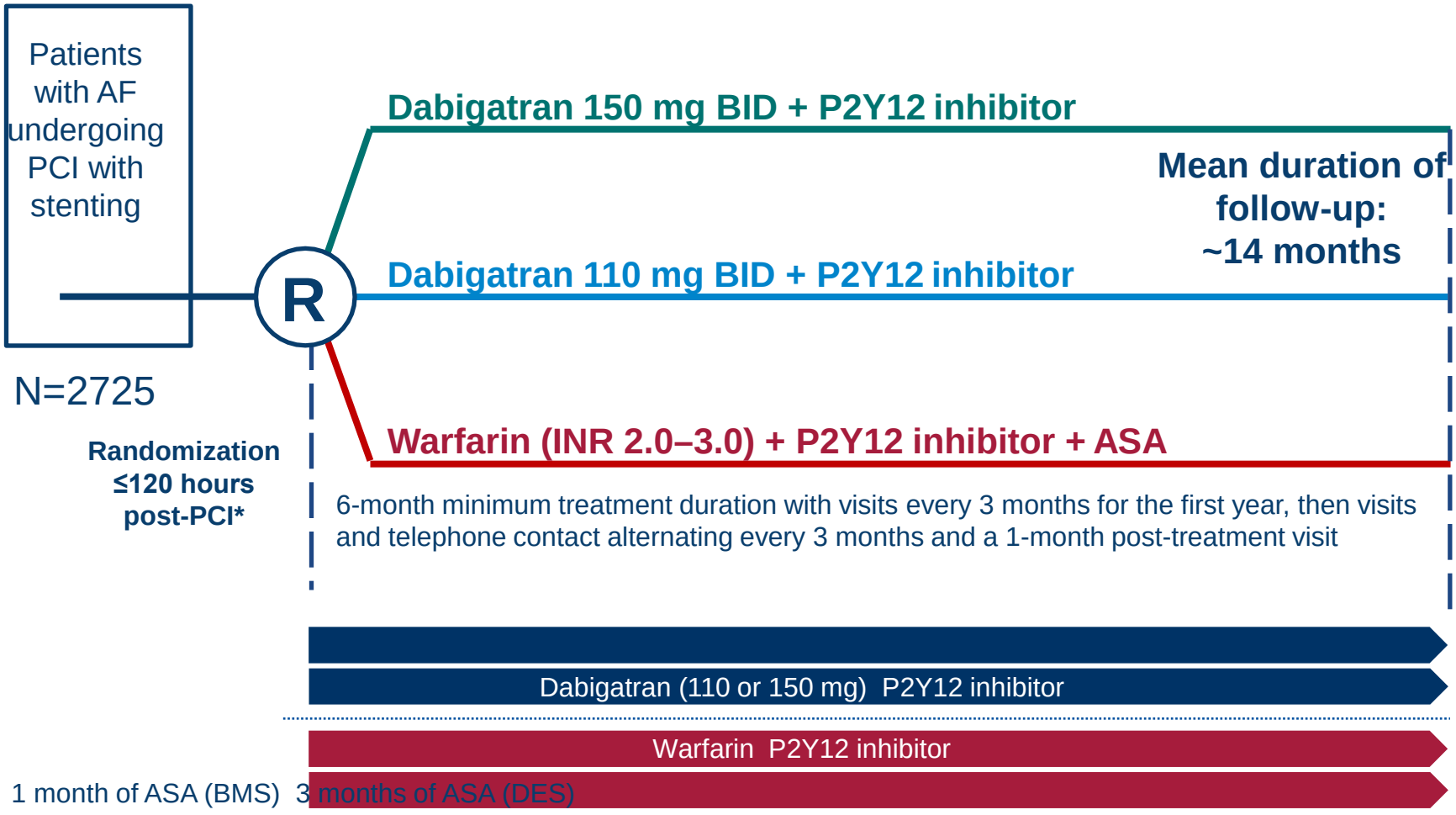
* The hazard ratios were calculated by the Cox proportional-hazards model for time to the first event, stratified according to indication at enrollment and either the antiplatelet regimen (in the analysis of the anticoagulant-regimen comparison) or the anticoagulant regimen (in the analysis of the antiplatelet-regimen comparison). All P values for superiority are two-sided. ISTH denotes International Society on Thrombosis and Haemostasis, NS not significant, and NT not tested.

† The result of the noninferiority test comparing the time to the first primary safety event in the apixaban group with that in the vitamin K antagonist group was significant (P<0.001).

‡ This analysis had the first nonsignificant result in the hierarchical testing procedure for the outcomes assessed in the anticoagulant-regimen comparison.

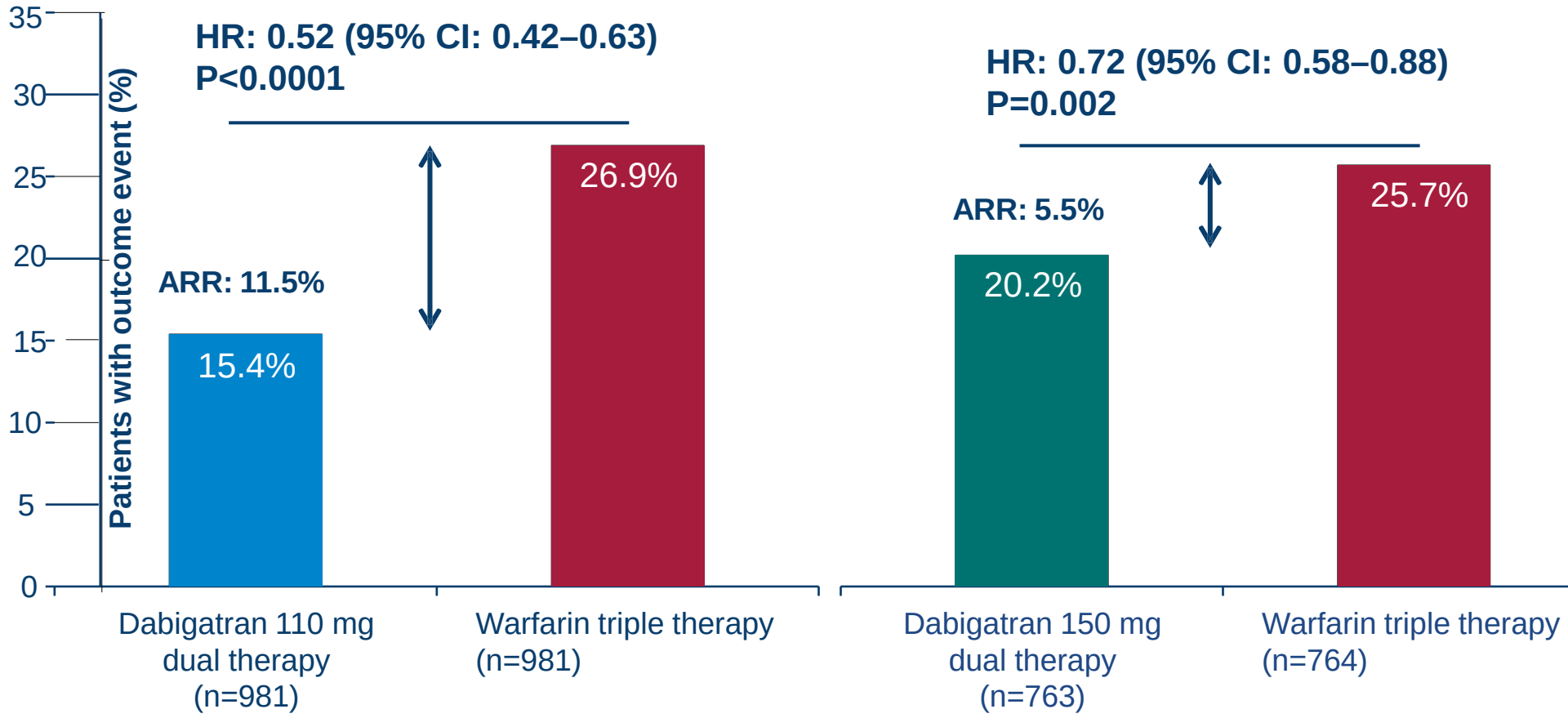
§ This analysis had the first nonsignificant result in the hierarchical testing procedure for the outcomes assessed in the antiplatelet-regimen comparison.

Re-Dual PCI



***Study drug should be administered 6 hours after sheath removal and no later than ≤120 hrs post-PCI (≤72 hrs is preferable).** PROBE, prospective, randomized, open, blinded end-point; R, randomization; BMS, bare metal stent; DES, drug-eluting stent. ClinicalTrials.gov: NCT02164864; Cannon et al. Clin Cardiol 2016

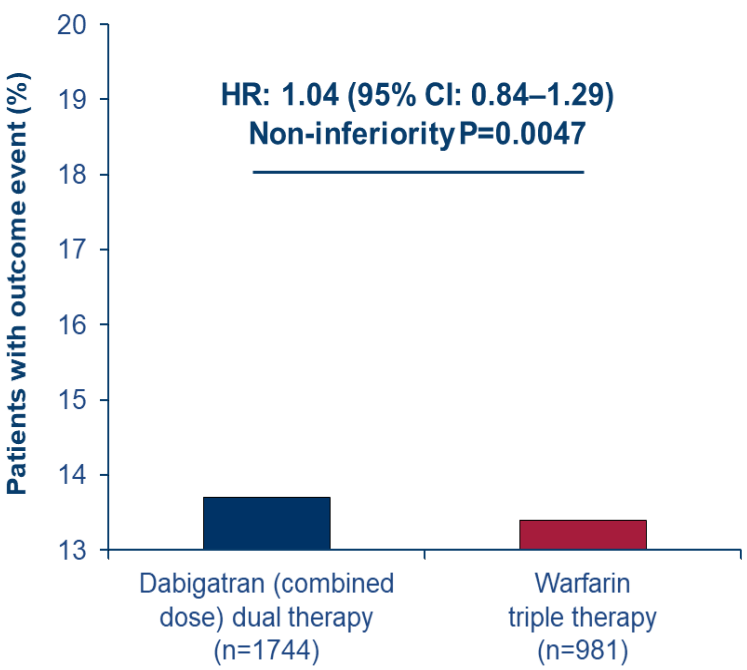
Primary endpoint: ISTH major or clinically relevant non-major bleeding event

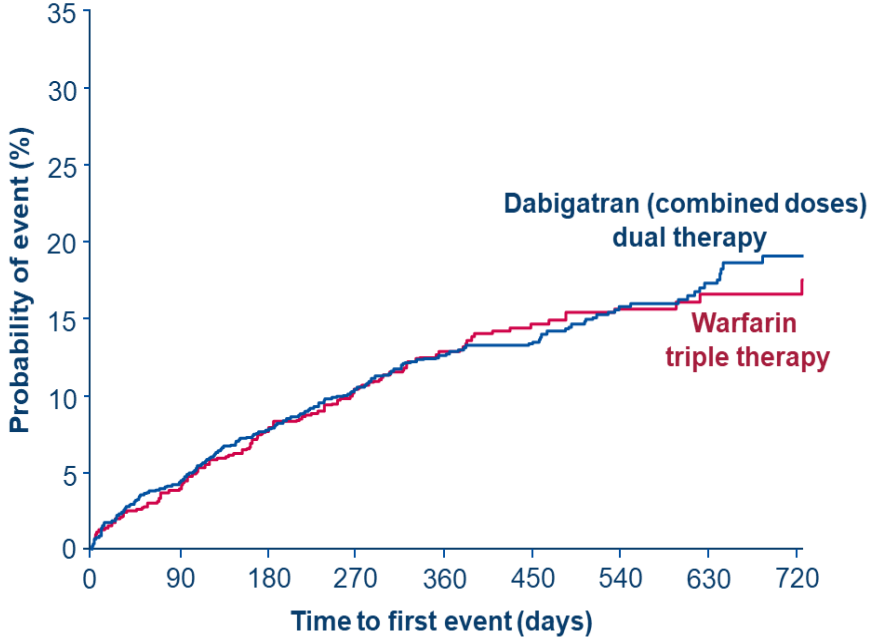


Wald two-sided P value from (stratified) Cox proportional-hazard model (alpha=0.05). ARR, absolute risk reduction

Time to death or thromboembolic event, or unplanned revascularization

RE-DUAL PCI
Study in NVAF patients undergoing PCI





Non-inferiority P value is one sided (alpha=0.025). Results presented are Step 3 of hierarchical testing procedure, testing non-inferiority of dabigatran dual therapy (combined doses) to warfarin triple therapy in death or thromboembolic event and unplanned revascularization

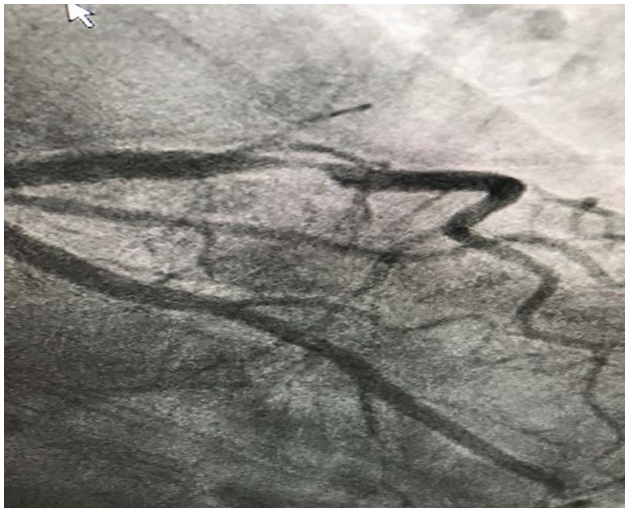
Aspirin can be omitted in most patients post PCI with AFIB

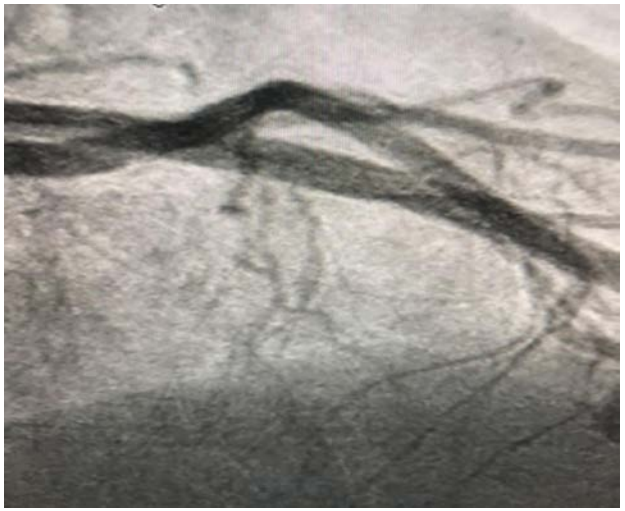
- Dual therapy without aspirin bests triple therapy with aspirin

- WOEST trial (warfarin)
- PIONEER AF Trial (rivoroxaban 15mg)
- Re-Dual PCI (dabigatran)
- Augustus Trial (apixiban)

Case Study

- 58 year old male with stable angina undergoes cath and a severe LAD stenosis is found. A 3rd generation drug eluting stent is placed. What is the *minimum* Class I *recommended* time for continuation of dual antiplatelet therapy?
- A. 1 month
- B. 3 months
- C. 6 months
- D. 12 months

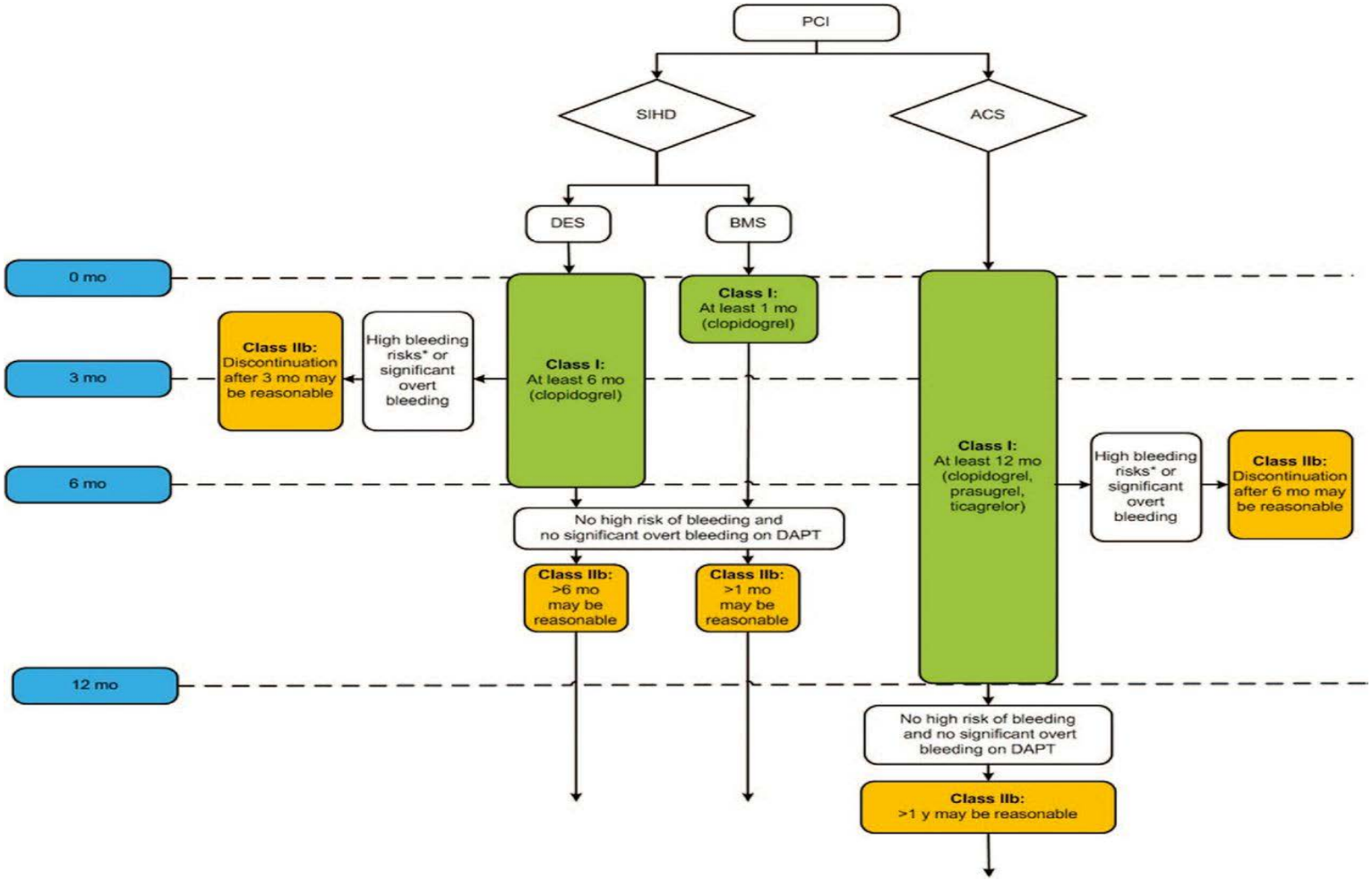




- 58 year old male with stable angina undergoes cath and a severe prox LAD stenosis is found. A 3rd generation drug eluting stent is placed. What is the minimum *guideline recommended* time for continuation of dual antiplatelet therapy?

- A. 1 month
- B. 3 months
- **C. 6 months**
- D. 12 months

Algorithm for DAPT duration in PCI

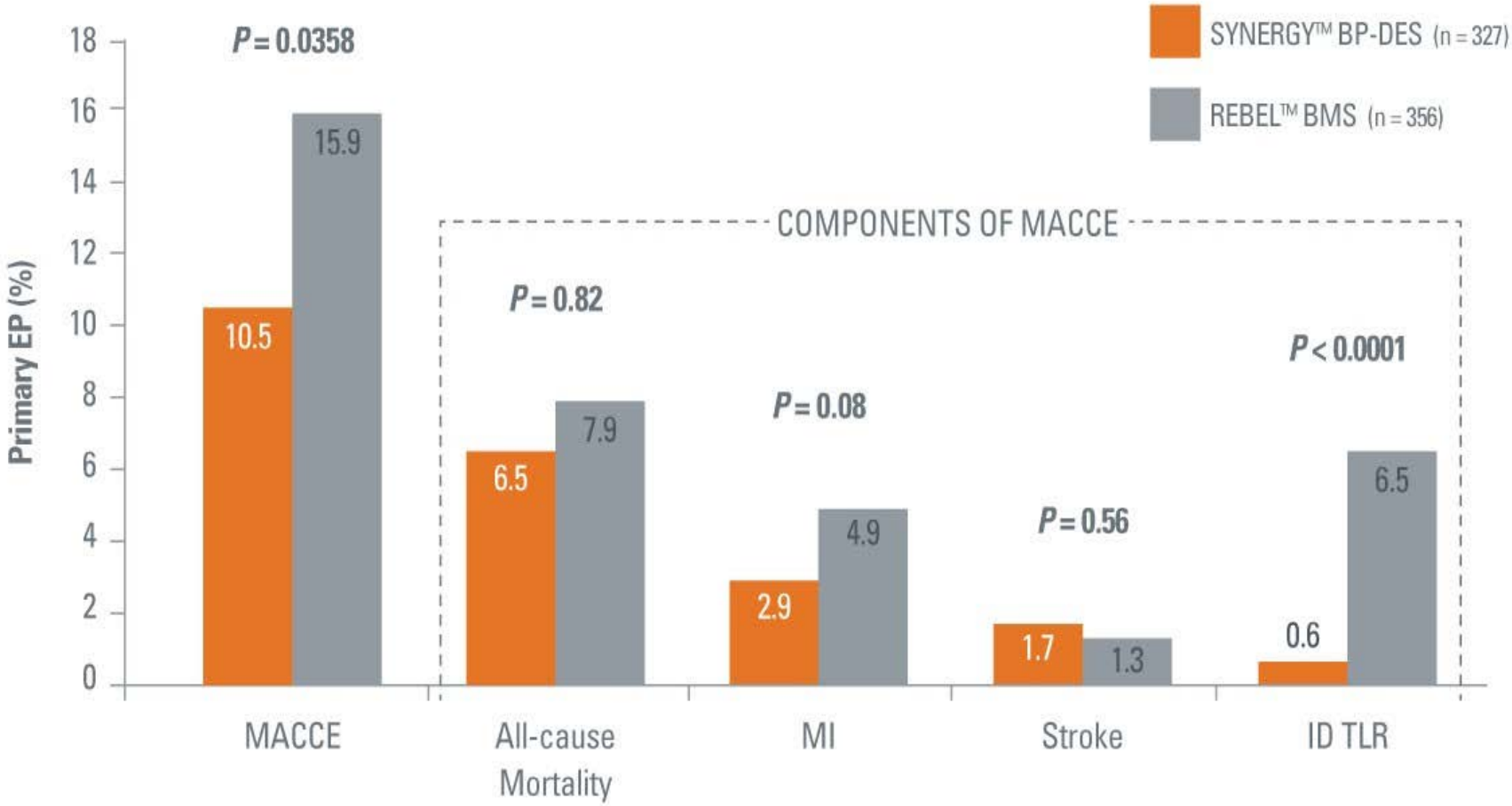


2016 ACC/AHA guidelines

Senior Trial

One-Month DAPT Discontinuation Cohort

0 stent thromboses after DAPT discontinuation



Onyx ONE Global Study Design

Prospective, Multicenter, Single-blind Randomized Trial

High Bleeding Risk patients undergoing PCI
(no lesion, vessel limitations)

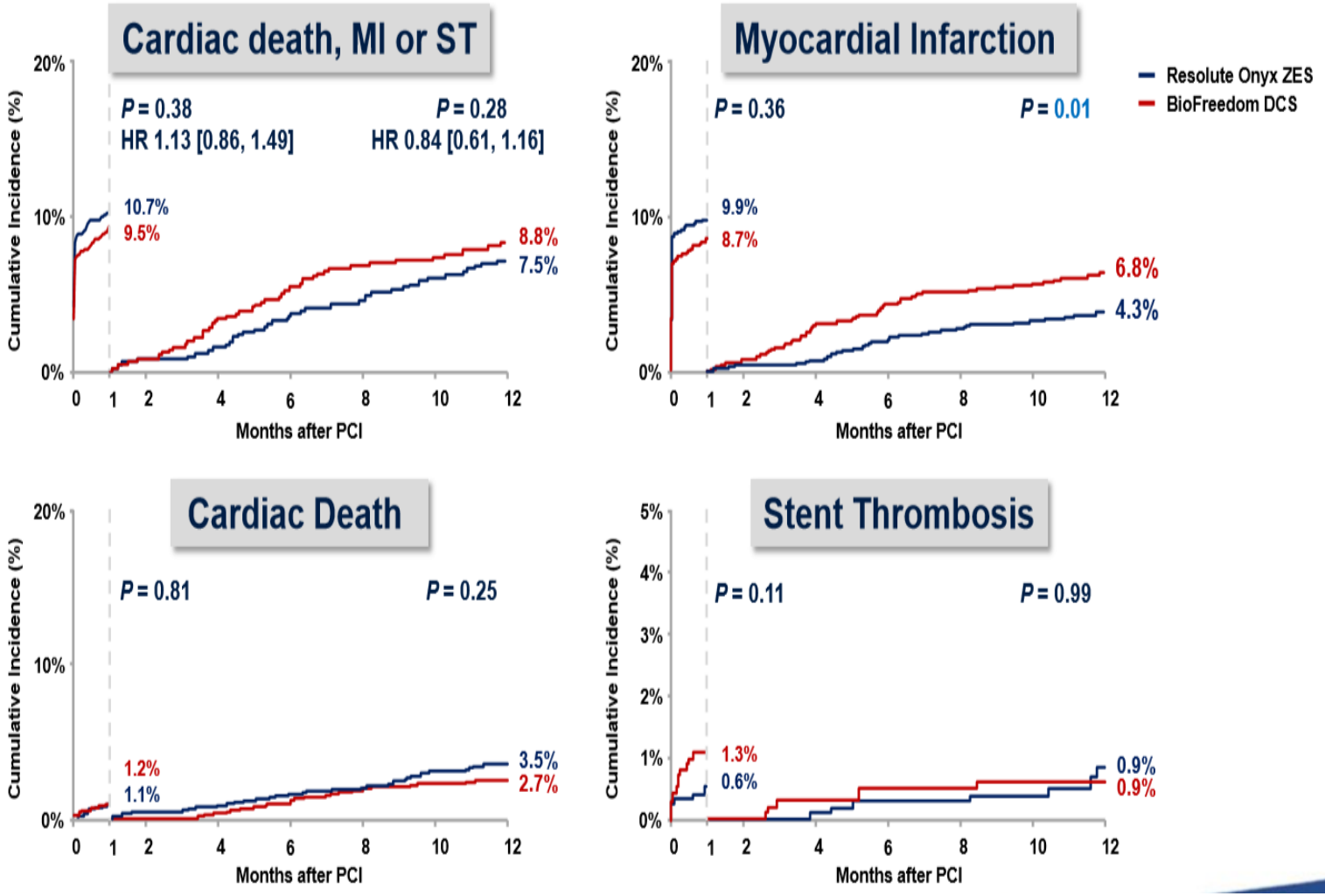
Resolute Onyx™ ZES
with 1 Month DAPT
(N=1000)

1:1 randomization
84 global sites
Enrollment Nov 2017 – Sep 2018

BioFreedom™ DCS
with 1 Month DAPT
(N=1000)

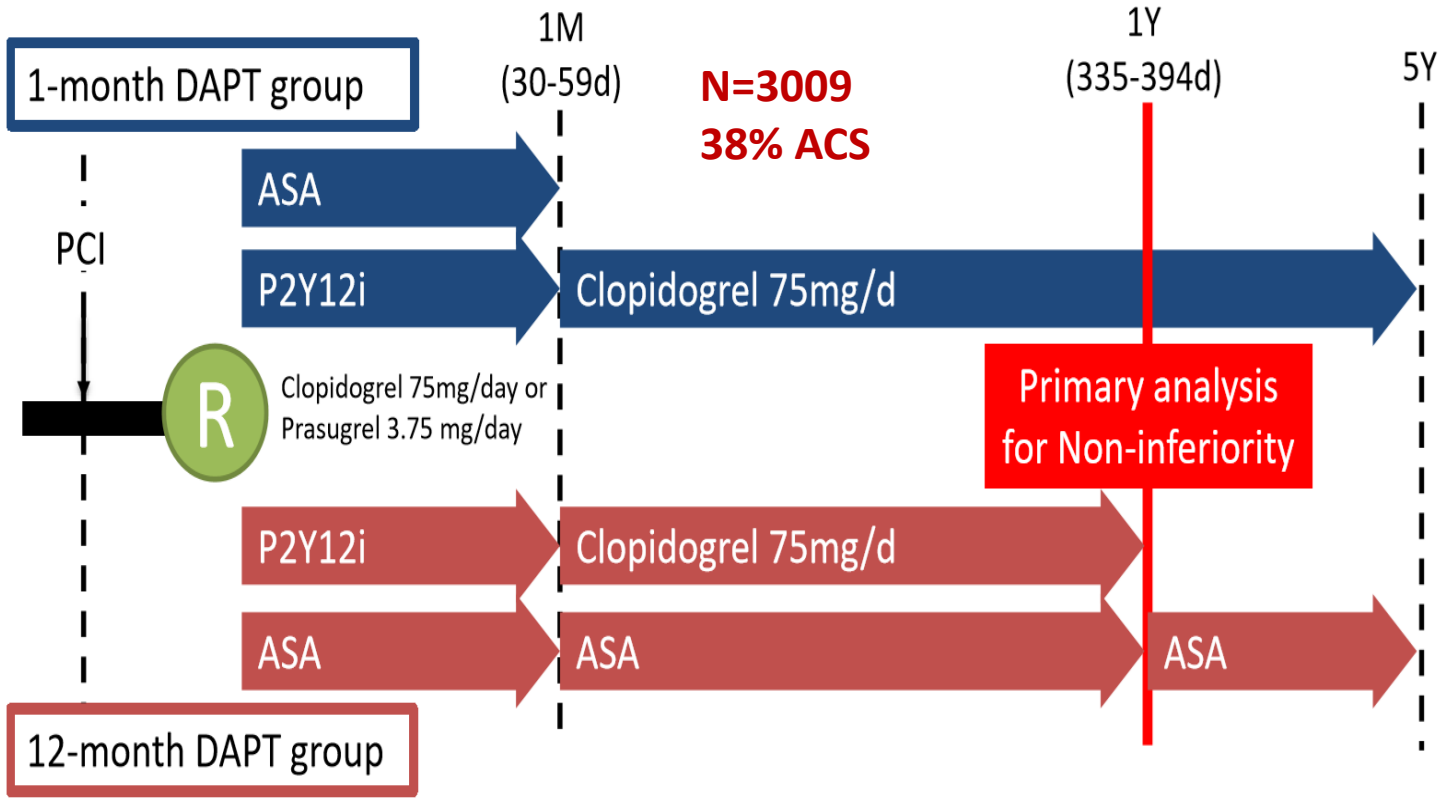
Primary safety endpoint:	Cardiac death, MI or stent thrombosis (def/prob) at 1 year
2° Efficacy endpoint (powered):	Target Lesion Failure (TLF; cardiac death, TV-MI or cd-TLR) at 1 year
Other secondary endpoints:	Lesion, device and procedure success rates, BARC bleeding, individual components of primary endpoints

One-Month Landmark Analyses (Time of DAPT Discontinuation)



STOPDAPT-2:

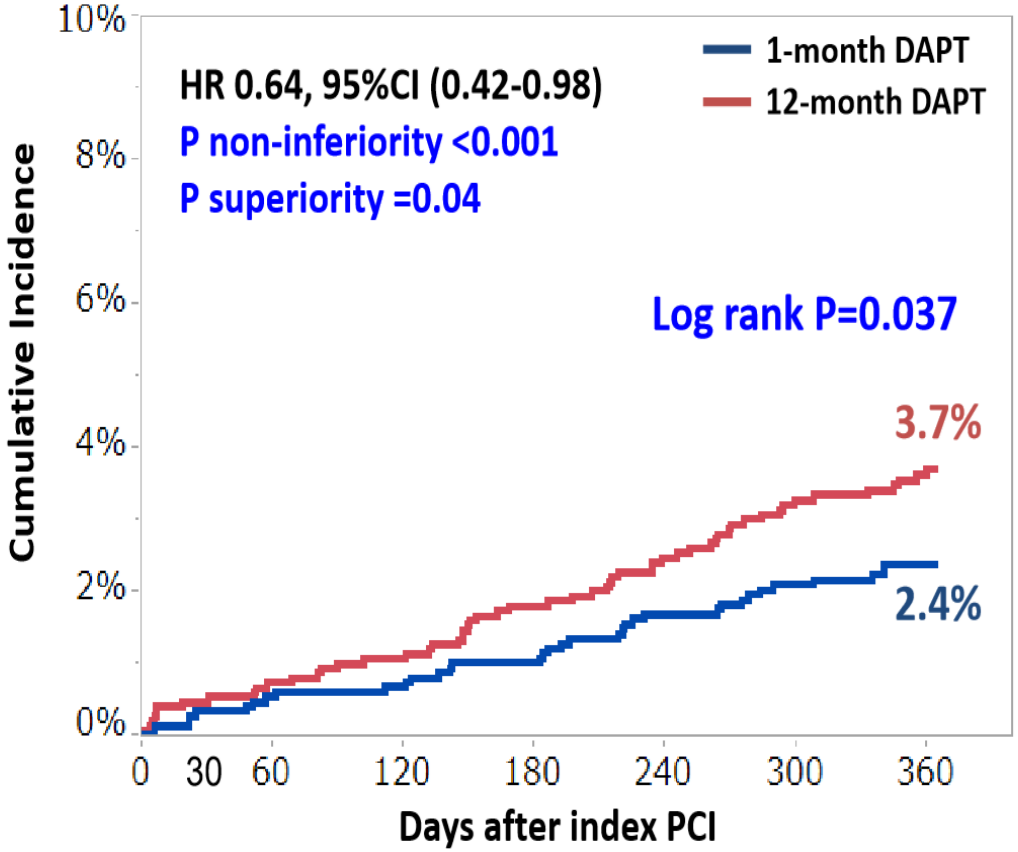
Prospective multicenter open-label randomized trial comparing 1-month versus 12-month DAPT after CoCr-EES implantation with limited exclusion criteria.



JAMA 2019

Primary Endpoint: Net clinical benefit

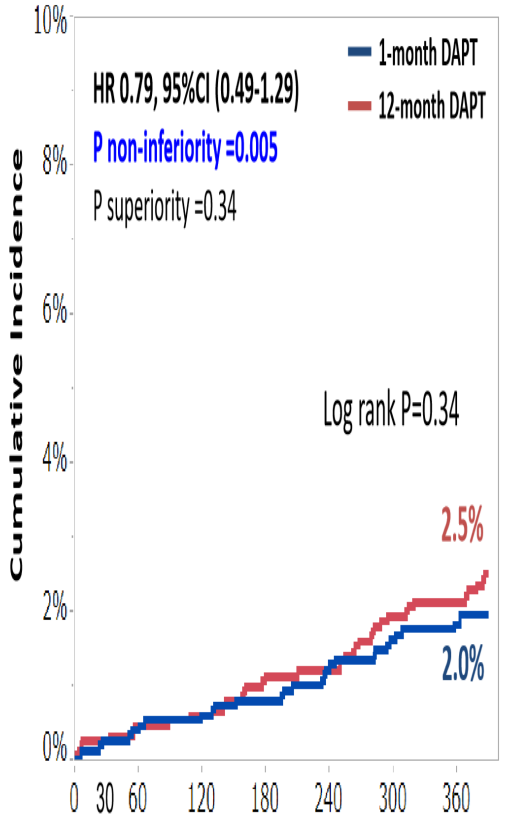
CV death/MI/ST/Stroke/TIMI major/minor bleeding



No. at risk								
12-month DAPT	1509	1501	1486	1481	1469	1458	1442	1159
1-month DAPT	1500	1494	1479	1475	1468	1453	1441	1151

Major secondary ischemic endpoint

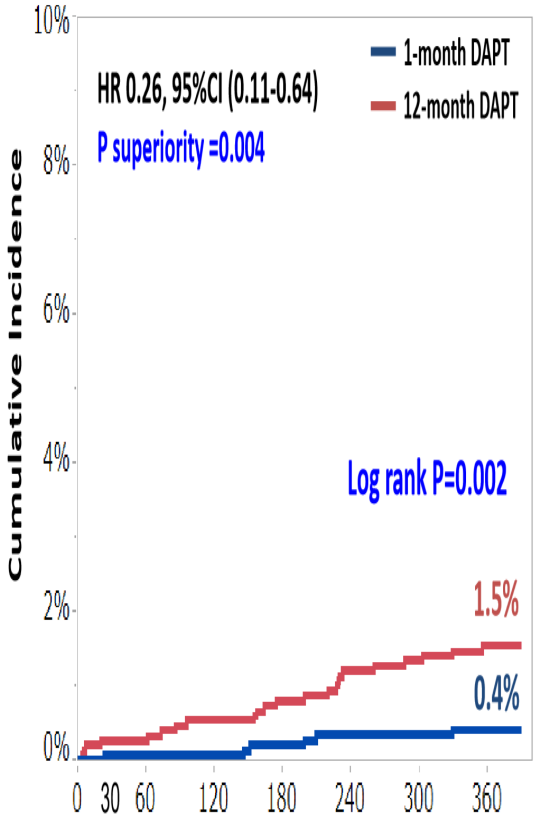
CV death/MI/ST/Stroke



No. at risk								
12-month DAPT	1509	1504	1490	1488	1479	1473	1458	1172
1-month DAPT	1500	1495	1480	1476	1471	1458	1446	1157

Major secondary bleeding endpoint

TIMI major/minor bleeding

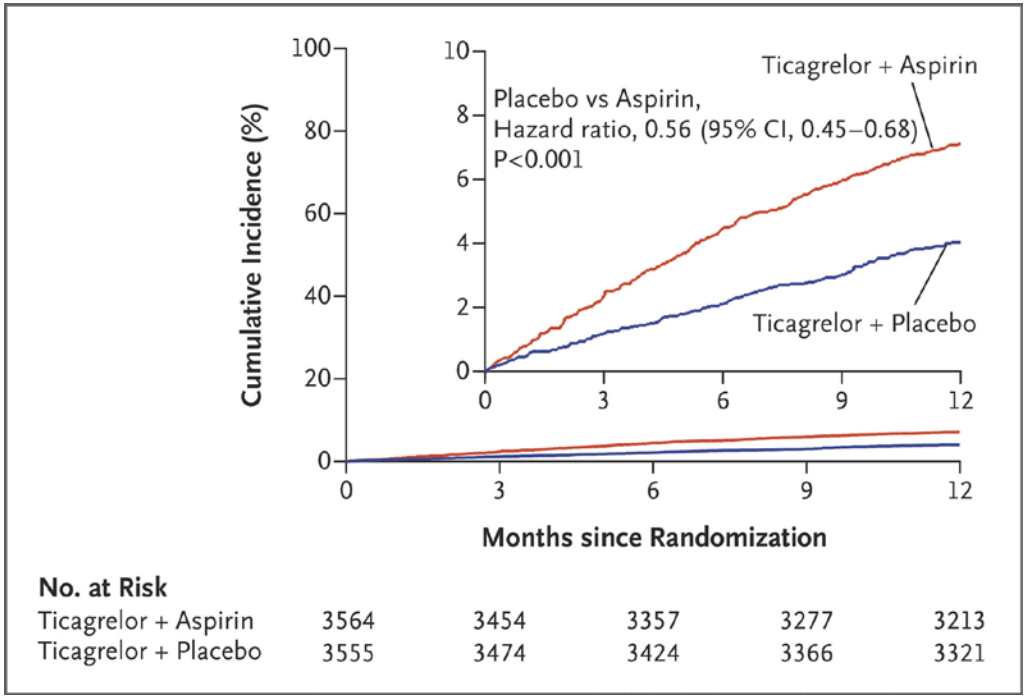


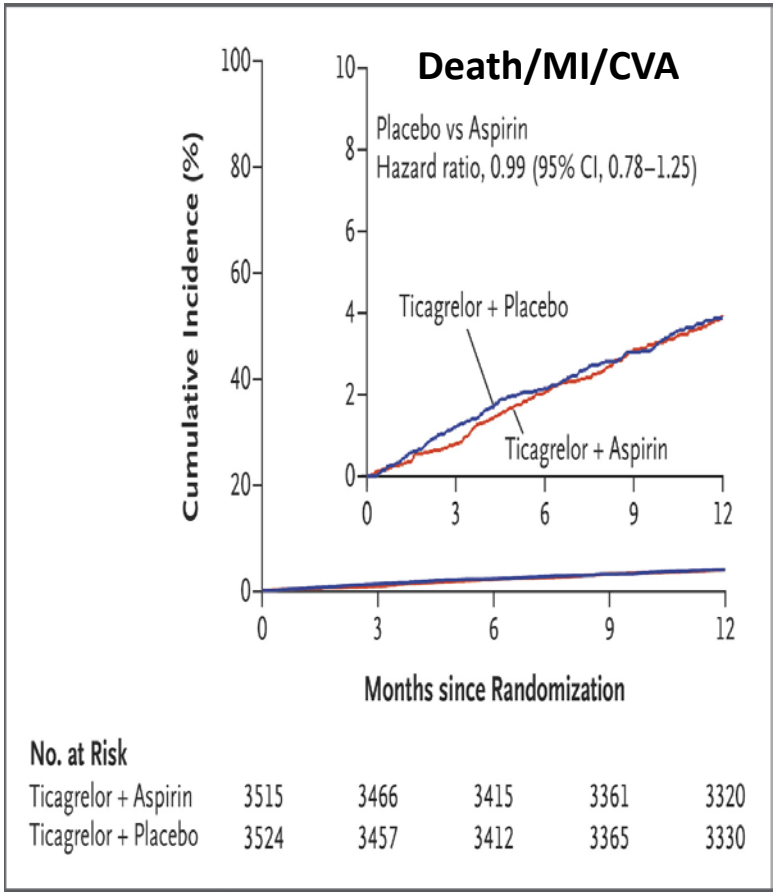
No. at risk								
12-month DAPT	1509	1504	1491	1487	1480	1471	1462	1180
1-month DAPT	1500	1495	1483	1481	1477	1467	1457	1166

Twilight Trial (N =7119)

60% unstable angina/NSTEMI

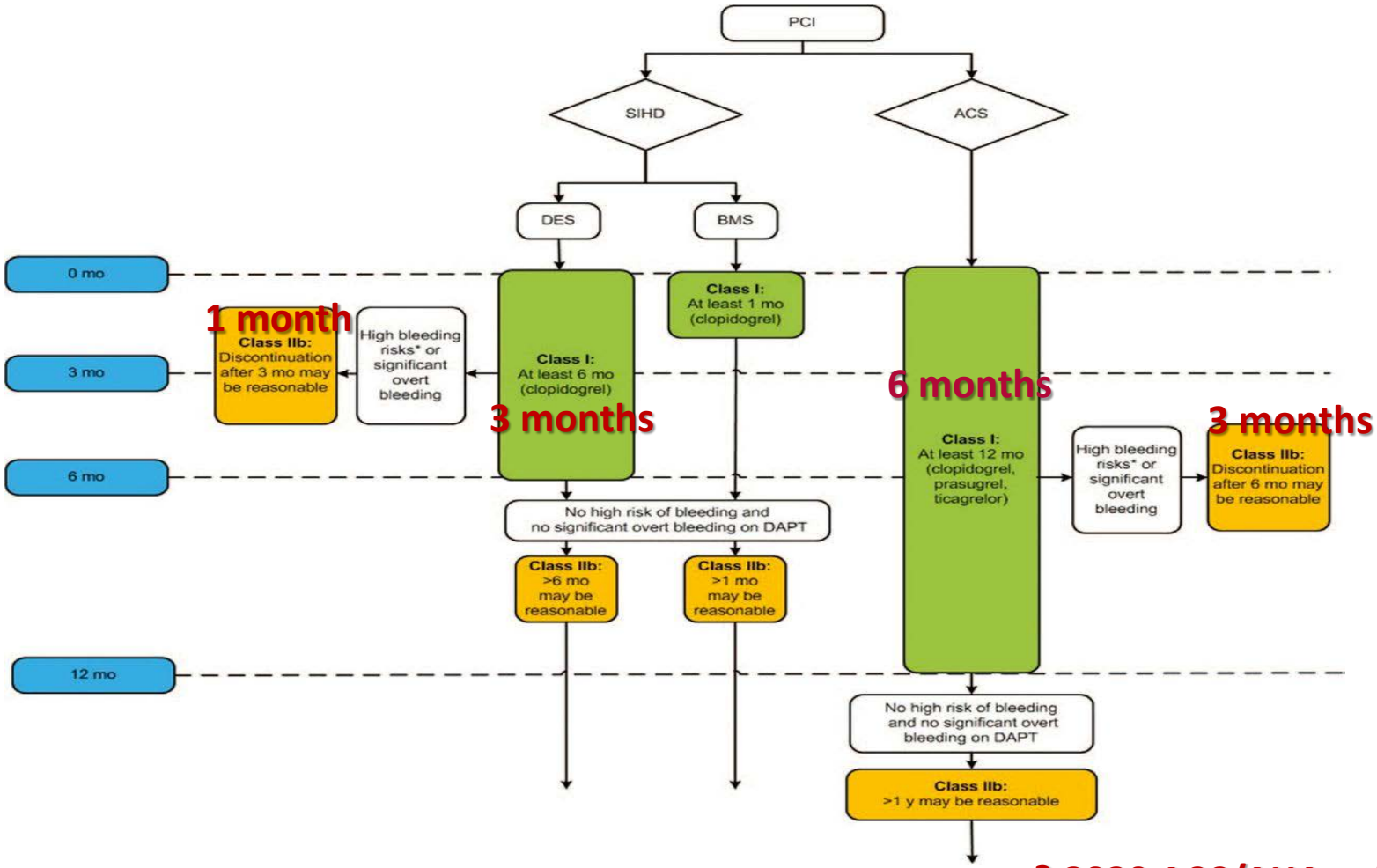
Discontinuation of ASA 3 months post PCI; Ticagrelor monotherapy





NEJM 2019

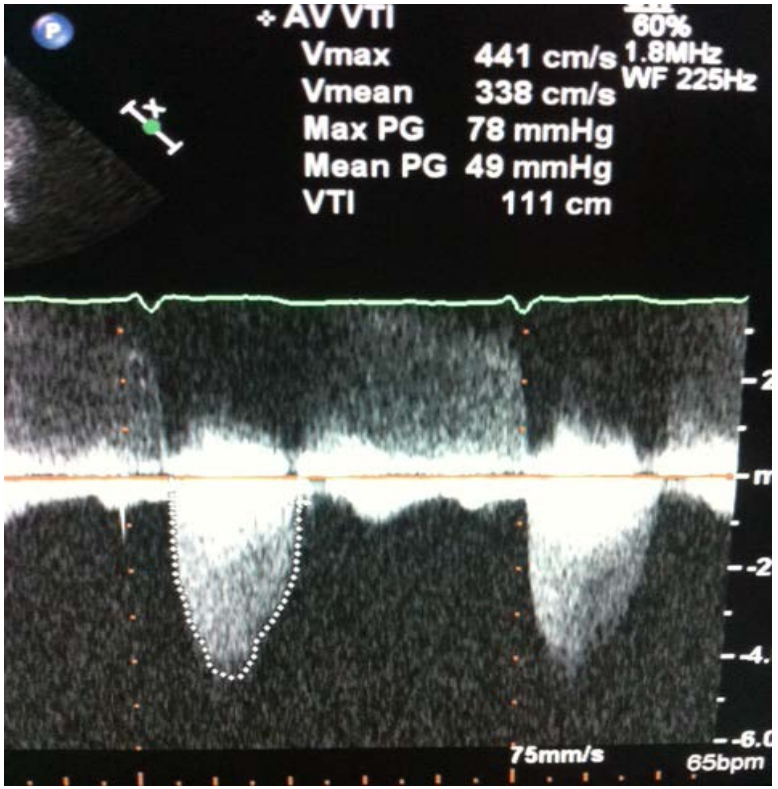
Algorithm for DAPT duration in PCI



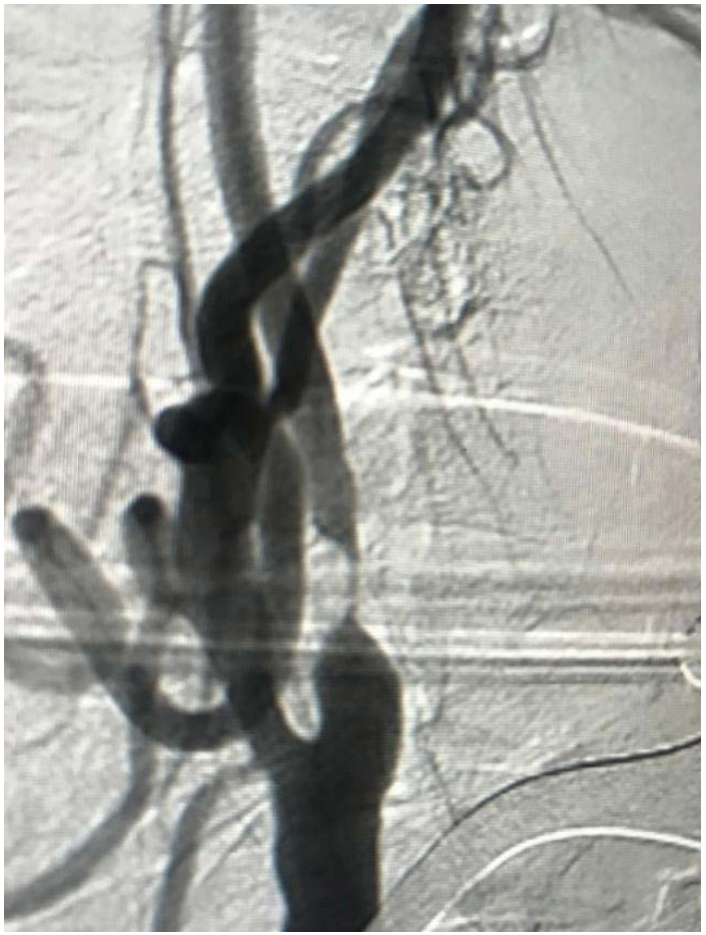
? 2020 ACC/AHA guidelines

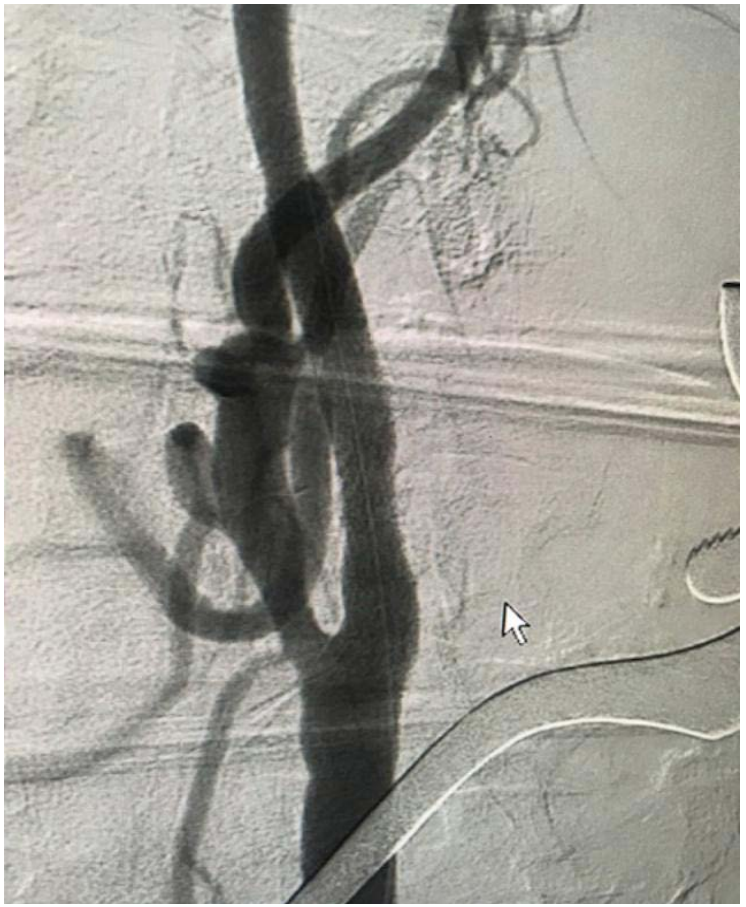
Interesting Case

- 82 year old male admitted with TIA – transient dysarthria.
- Left carotid bruit. Systolic murmur on exam
- EKG: AFIB

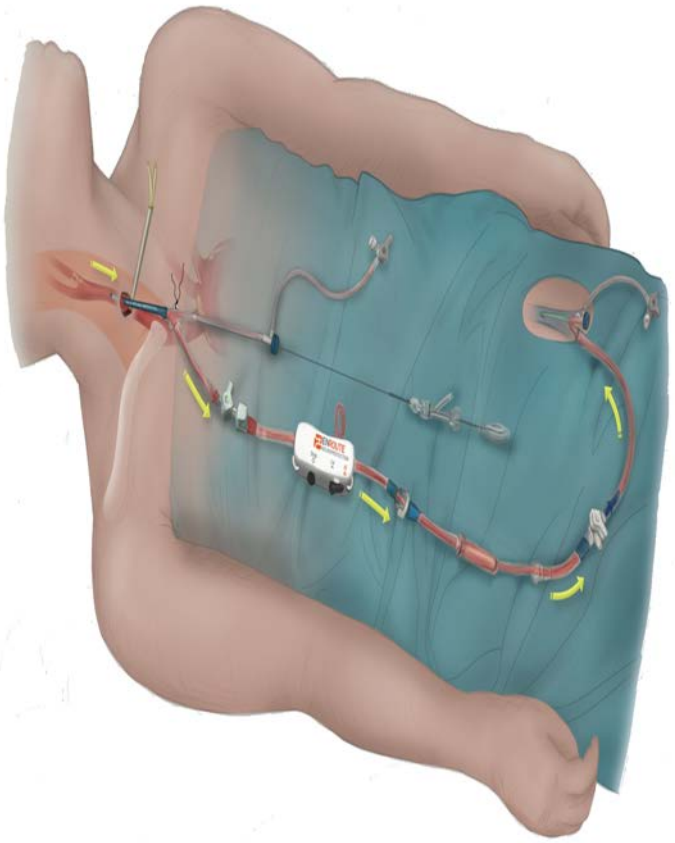


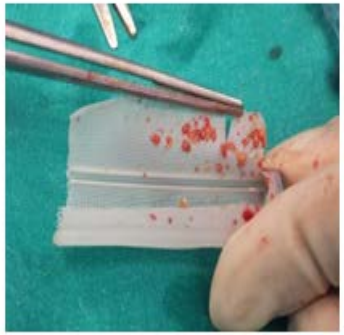
Severe LICA stenosis



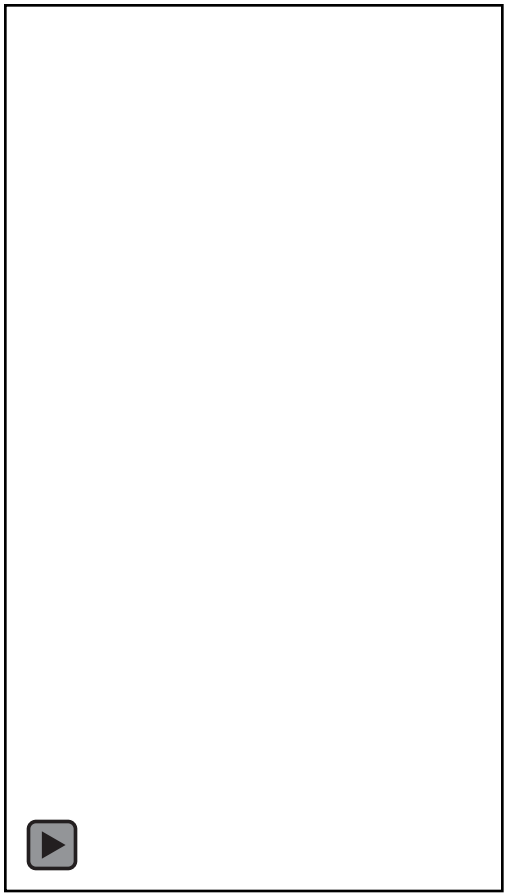


Transcarotid Stenting: Flow Reversal



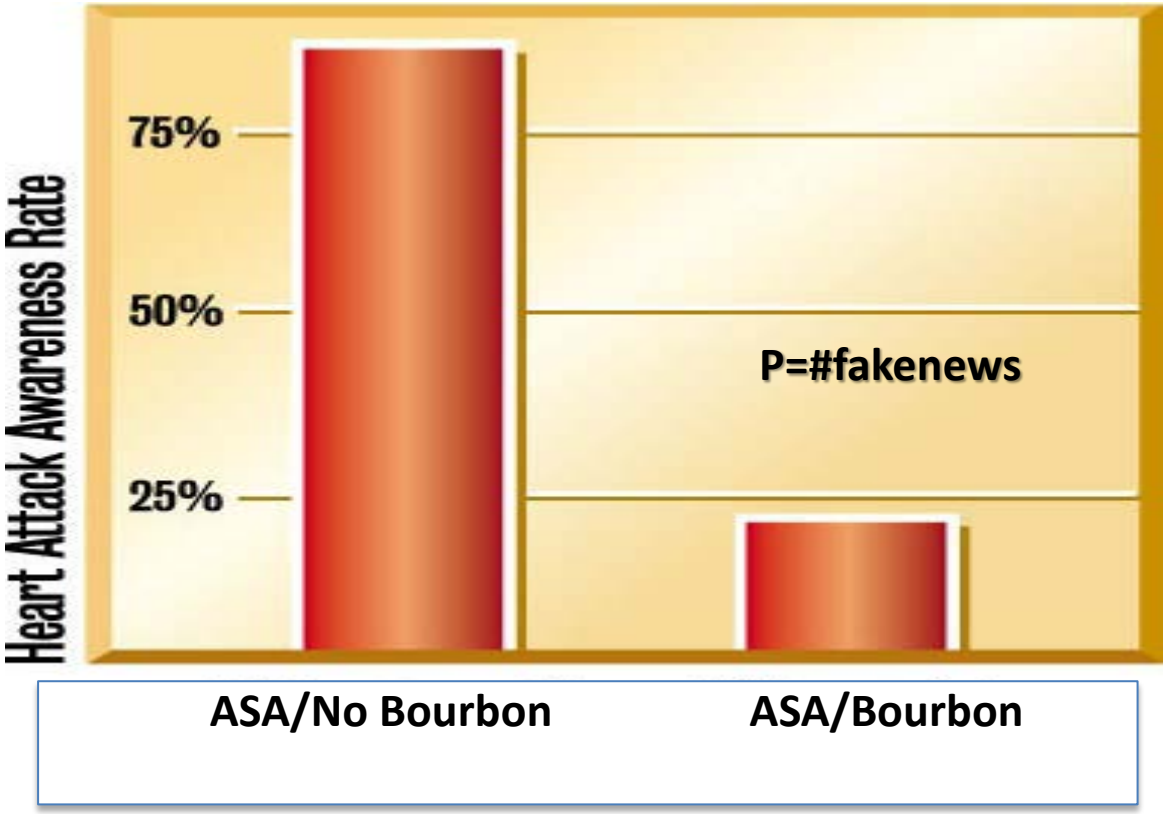


2 weeks later: TAVR



Discharge Regimen:
Plavix 75mg/day
Eliquis 5mg BID
No ASA

Heart Attack Awareness



Test subjects administered a single aspirin tablet in the morning, followed by a fifth of Kentucky bourbon over the next several hours, were 85 percent less likely to realize they were having a heart attack than subjects who did not take bourbon with aspirin.

Study sponsor

Source: theonion.com

Conclusions

- Aspirin for primary prevention should be cautiously used in highly selected patients(age 40-70) at low bleeding risk.

- Aspirin can be omitted in most patients who require chronic anticoagulation for AFIB.

- Ongoing trials are evaluating ways to minimize dual antiplatelet therapy to reduce the risk of bleeding events without an increase in ischemic complications in post PCI patients.