Who Should be on Aspirin and Why?
Disclosures

Research Support:
Janssen, BMS/Pfizer, Idorsia, Daichi-Sanyo, Stago, Recovery Force (Via NIH SBIR).

Educational Grant: Janssen
Who Should be on Aspirin and Why?

1. Why did we get here?
2. Proactive or Reactive
3. As an Adjuvant
Clot Formation
The Inseparable Relation Between Platelet Function and Coagulation

AT III = Antithrombin III
Xa = Factor Xa
PAF = Platelet Activating Factor
TxA₂ = Thromboxane A₂
ADP = Adenosine Diphosphate
LMWH = Low-molecular-weight Heparin

GP Iib-IIia inhibitors displace fibrinogen in existing thrombi and prevent further platelet cross-linking and thrombosis.
Platelet Activation Pathways

- **Vorapaxar**
  - Thrombin
  - PAR-1
  - PAR-4

- **Aspirin**
  - Tx A2 Receptor

- **Eptifibatide**
  - GP IIb/IIIa Receptor (Platelet Aggregation)

- **Abciximab**
  - Tirofiban

- **GP VI and α2β1 Receptors**
  - (Collagen)
  - (Platelet Activation/Adhesion)

- **GP Ib/V/IX**
  - (von Willebrand factor)
  - Receptor (Platelet Adhesion)

- **Ticlopidine**
- **Clopidogrel**
- **Prasugrel**
- **Ticagrelor**
- **Elinogrel**
- **Cangrelor**
- **Selatogrel**
- **Vorapaxar**
Why did we get here

1974
Trend on Reduced mortality after AMI

1988
ISIS 2. Positive trial on Secondary prevention (28d)
Trend on Reduced mortality after AMI

1989
FDA. No ASA primary prev

1998
FDA. No ASA primary prev

2001
PPP N=4495

2005
WHN N=39876

2008
POPADAD
N=1276
JPAD
N=2539

2010
AAA N=3350

2014
FDA. No ASA primary prev

2019
ARRIVE
N=12546
ASCEND
N=15480
ASPREE
N=19114
### 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIb</td>
<td>A</td>
<td>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.^[61-61, 61-61-61, 61-61-61-61]</td>
</tr>
<tr>
<td>III: Harm</td>
<td>B-R</td>
<td>2. Low-dose aspirin (75-100 mg orally daily) should not be administered on a routine basis for the primary prevention of ASCVD among adults &gt;70 years of age.^[61-61, 61-61-61, 61-61-61-61]</td>
</tr>
<tr>
<td>III: Harm</td>
<td>C-LD</td>
<td>3. Low-dose aspirin (75-100 mg orally daily) should not be administered for the primary prevention of ASCVD among adults of any age who are at increased risk of bleeding.^[61-61, 61-61-61, 61-61-61-61]</td>
</tr>
</tbody>
</table>

Circulation. 2019;140:e596–e646
NEW DEVELOPMENTS

STUDIES: LOW-DOSE ASPIRIN RISK MAY OUTWEIGH BENEFITS

Dr. Sanjay Gupta | On Twitter: @drsanjaygupta
A 63 YOM former smoker with HTN and DM, SP CABG is on ASA 81 daily. Has no history of major bleeding. He heard about the new guidelines.

Doctor, I stopped using asa.

a) I agree, CNN is right
b) Please resume asa
Who Should be on Aspirin and Why?

1. Why did we get here?
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For MACE/MALE secondary prevention the ASA benefit outweighs the Bleed risk

BMJ 2002;324:71–86
REACTIVE ASA VTE

For VTE secondary prevention, MAY also consider ASA
A 62 YOWF with HTN, 6 y of DM and hypothyroidism. Has been taking asa 81 mg for 5 y. She has no Hx of PAD or CAD.

She heard about the new guidelines.

Doctor, I stopped using asa.

a) I agree, CNN is right

b) Please resume asa
**PROACTIVE ASA MACE**

**Benefits and Risks of Low-Dose Aspirin in Primary Prevention Trials**

Risk of Serious Vascular Events vs. Bleeding Risk

<table>
<thead>
<tr>
<th>Low-Risk</th>
<th>Moderate-Risk</th>
<th>High-Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNT= 500-1,000</td>
<td>ASCEND NNT= 91; NNH= 112</td>
<td>NNT= ≤100</td>
</tr>
<tr>
<td>NNH= 500-1,000</td>
<td>ARRIVE NNT=126; NNH= 196</td>
<td>NNH= 500-1,000</td>
</tr>
<tr>
<td>Consider aspirin evaluating potential benefits and risks</td>
<td>ASPREE NNT=100; NNH=100</td>
<td>Use aspirin routinely unless contraindicated</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Trial</th>
<th>NNT</th>
<th>NNH</th>
<th>NNH/NNT</th>
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<tbody>
<tr>
<td>COMPASS</td>
<td>77</td>
<td>83</td>
<td>1.07</td>
</tr>
<tr>
<td>PEGASUS TIMI 54</td>
<td>79</td>
<td>106</td>
<td>1.34</td>
</tr>
<tr>
<td>ASCEND</td>
<td>91</td>
<td>112</td>
<td>1.38</td>
</tr>
<tr>
<td>ARRIVE</td>
<td>126</td>
<td>196</td>
<td>1.55</td>
</tr>
<tr>
<td>ASPREE</td>
<td>100</td>
<td>100</td>
<td>1</td>
</tr>
</tbody>
</table>

*NorthShore University HealthSystem*
<table>
<thead>
<tr>
<th>Guideline</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>2016 USPSTF</td>
<td>Recommend low-dose aspirin use for the primary prevention of CVD and CRC in adults aged 50 to 59 years who have a 10% or greater 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years (grade B)</td>
</tr>
<tr>
<td>2016 ESC</td>
<td>Recommend against initiating aspirin in individuals without overt cardiovascular disease (class III)</td>
</tr>
<tr>
<td>2016 EASD</td>
<td>Antiplatelet therapy (e.g., with aspirin) is not recommended for people with DM who do not have CVD (class IIIA)</td>
</tr>
<tr>
<td>2019 AHA/ACC</td>
<td>Recommend against aspirin in individuals older than 70 years and provide a weak recommendation (class IIb) that aspirin might be considered among adults aged 40–70 years</td>
</tr>
<tr>
<td>2019 NICE</td>
<td>Recommend against aspirin for the primary prevention of CVD. Consider prescribing aspirin in people with a high risk of stroke or myocardial infarction</td>
</tr>
<tr>
<td>2019 ADA</td>
<td>Recommend aspirin therapy (75–162 mg/day) for primary prevention strategy in those with diabetes who are at increased cardiovascular risk, after a discussion with the patient on the benefits versus increased risk of bleeding. Aspirin is not recommended for those at low risk of ASCVD (such as men and women aged ≤50 years with diabetes with no other major ASCVD risk factors) as the low benefit is likely to be outweighed by the risks of bleeding</td>
</tr>
</tbody>
</table>
The event rate was much lower than expected, which is probably reflective of contemporary risk management strategies, making the study more representative of a low-risk population.

Lancet 2018; 392: 1036–46

**ARRIVE Trial**

**Primary endpoint occurred**
- 4.29% for ASA
- 4.48% for placebo

HR 0.96; 95% CI 0.81–1.13; p=0.6038

**Gastrointestinal bleeding**
- 0.97% for ASA
- 0.46% for placebo

HR 2.11; 95% CI 1.36–3.28; p=0.0007

**Male patients**
- 55 years and older
- and had between two and four risk factors

**Female patients**
- 60 years or older
- and had three or more risk factors.

**Average cardiovascular risk**
(10-y risk of CHD 10–20%)
Rate of cardiovascular disease
10.7 events per 1000 person-years in the aspirin
11.3 events per 1000 person-years in the placebo
HR 0.95; 95%CI 0.83 to 1.08

Major hemorrhage
8.6 events per 1000 person-years
6.2 events per 1000 person-years
HR 1.38; 95% CI, 1.18 to 1.62

• 70 years of age or older
  (or ≥65 y-o among blacks and Hispanics in the US).

Free of: CAD, CVD, AF, Dementia or physical disability, high bleed risk

Composite of Death, Dementia, Physical disability was not different

Serious vascular events
Aspirin  8.5%
Placebo  9.6%
RR  0.88; 95%CI 0.79 to 0.97

Major bleeding
Aspirin  4.1%
Placebo  3.2%

RR  1.29; 95% CI, 1.09 to 1.52
(Most of the excess being gastrointestinal bleeding)

Outcomes on cancer are still expected.

TUMOR GROWTH
- Growth factors
- Angiogenesis
- Granulocytes recruitment

IMMUNE ESCAPE
- Platelet-cancer cell aggregates
- Platelet-fibrin deposition
- Blocking NK cell-mediated cytosis

EXTRAVASATION
- MMP production
- MMP-mediated matrix degradation
- Vessel permeability
- EMT induction

Low-dose aspirin

Normal mucosa

Adenoma

Carcinoma

Epithelial-Mesenchimal Transition

Invasive and metastatic cancer cells
Who Should be on Aspirin and Why?

1. Why did we get here?
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A 66 YO Hispanic male with atrial fibrillation, DM, HTN arrives to the office 3 w after LAD DES due to NSTEMI. Has no Hx of stroke

He is currently on Apixaban 5 mg BID + Clopidogrel 75 mg daily and ASA 81.

a) Stop asa

b) Continue asa
In Triple Therapy?

- TRIPLE Therapy
  - VKA+ASA + Clopi
  - Short as possible

- TRIPLE Therapy
  - OAC+ASA + P2Y12

- OAC+ASA + P2Y12
  - Lower INR
  - DOAC lowest dose

- OAC+ASA + P2Y12
  - DOAC pref?
  - 1 vs 6 mo

- (D)OAC+ ASA+ P2Y12
  - 1 mo

- OAC+ Clopi

- OAC+ Clopi

- OAC+ Clopi

- DUAL
  - OAC+ Clopi

Saito et al Journal of Cardiology 2019
### DAPT

### P2Y12

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Apixaban</th>
<th>Vitamin K Antagonist</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value for Superiority</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anticoagulation-regimen comparison</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISTH major or clinically relevant nonmajor bleeding†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients with event/total no. (%)</td>
<td>243/2290 (10.5)</td>
<td>332/2259 (14.7)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Event rate per 100 patient-yr</td>
<td>24.7</td>
<td>35.8</td>
<td>0.69 (0.58–0.81)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death or hospitalization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients with event/total no. (%)</td>
<td>541/2306 (23.5)</td>
<td>532/2308 (27.4)</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Event rate per 100 patient-yr</td>
<td>57.2</td>
<td>69.2</td>
<td>0.83 (0.74–0.93)</td>
<td>0.002</td>
</tr>
<tr>
<td>Death or ischemic event</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients with event/total no. (%)</td>
<td>154/2306 (6.7)</td>
<td>163/2308 (7.1)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Event rate per 100 patient-yr</td>
<td>14.3</td>
<td>15.3</td>
<td>0.93 (0.75–1.16)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Antiplatelet-regimen comparison</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISTH major or clinically relevant nonmajor bleeding</td>
<td>Aspirin</td>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients with event/total no. (%)</td>
<td>367/2277 (16.1)</td>
<td>204/2279 (9.0)</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Event rate per 100 patient-yr</td>
<td>40.5</td>
<td>21.0</td>
<td>1.89 (1.59–2.24)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death or hospitalization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients with event/total no. (%)</td>
<td>604/2307 (26.2)</td>
<td>569/2307 (24.7)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Event rate per 100 patient-yr</td>
<td>65.7</td>
<td>60.6</td>
<td>1.08 (0.96–1.21)</td>
<td>NS</td>
</tr>
<tr>
<td>Death or ischemic event</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients with event/total no. (%)</td>
<td>149/2307 (6.5)</td>
<td>168/2307 (7.3)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Event rate per 100 patient-yr</td>
<td>13.9</td>
<td>15.7</td>
<td>0.89 (0.71–1.11)</td>
<td>NT</td>
</tr>
</tbody>
</table>

Patients in the apixaban group had a lower incidence of death or hospitalization than those in the vitamin K antagonist group (23.5% vs. 27.4%; hazard ratio, 0.83; 95% CI, 0.74 to 0.93; \( P=0.002 \))

Similar incidence of ischemic events.
 Patients in the aspirin group had an incidence of death or hospitalization and of ischemic events that was similar to that in the placebo group.
A 66 YO Hispanic male with CAD SP CABG 5 y ago, DM, HTN arrives to the office. He has a Hx of CLI and is SP SFA stent 1y ago, still claudicates but does not have rest pain.

He is on Rivaroxaban 2.5 and asa low dose

a) Stop asa

b) Continue asa
Rivaroxaban + aspirin vs. aspirin alone
Hazard ratio, 0.76 (95% CI, 0.66–0.86)
P<0.001
Rivaroxaban alone vs. aspirin alone
Hazard ratio, 0.90 (95% CI, 0.79–1.03)
P=0.12

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Year</th>
<th>Aspirin alone</th>
<th>Rivaroxaban alone</th>
<th>Rivaroxaban + aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin alone</td>
<td>9126</td>
<td>7808</td>
<td>3860</td>
<td>669</td>
</tr>
<tr>
<td>Rivaroxaban alone</td>
<td>9117</td>
<td>7824</td>
<td>3862</td>
<td>670</td>
</tr>
<tr>
<td>Rivaroxaban + aspirin</td>
<td>9152</td>
<td>7904</td>
<td>3912</td>
<td>658</td>
</tr>
</tbody>
</table>
Who Should be on Aspirin and Why?

1. Why did we get here?
2. Proactive or Reactive
3. As an Adjuvant