# Anti-thrombotic and anti-platelet therapy in primary and secondary prevention

## How thin can you go?

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# Presenter Disclosures

***Dr. John Graham*** **– Presenter**
***Topic:*** **Antithrombotic therapy in primary and secondary prevention**

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- **Patents:** N/A
- **Other:** N/A

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**Educational Objectives**

- Discuss indications for anti-platelet and anti-thrombotic therapy
  - Primary and secondary prevention
  - Combination therapy
- Targeted review of literature
- Tie this in with CCS guidelines
- Caveat
  - Moving target – this talk will likely be outdated in a month
  - Importance of individually tailored therapy being recognized
  - Recent research data of single anti-platelet therapy post ACS

## WHAT IS PREVENTION?

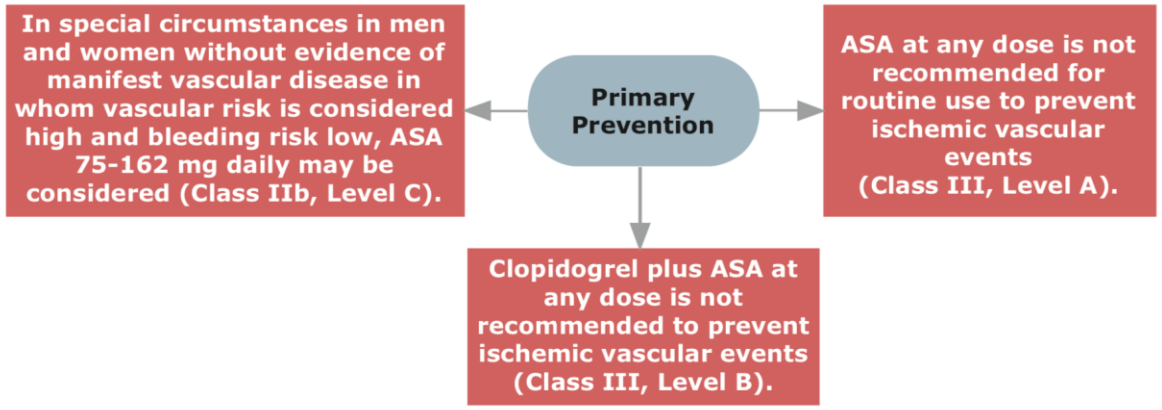
1. ***Primary Prevention***—intervening before health effects occur, through measures such as vaccinations, altering risky behaviors (poor eating habits, tobacco use), and banning substances known to be associated with a disease or health condition
2. ***Secondary Prevention***—screening to identify diseases in the earliest stages, before the onset of signs and symptoms (e.g. BP testing, CT angio, etc)
3. ***Tertiary Prevention***—managing disease post diagnosis to slow or stop disease progression through measures such as chemotherapy, rehabilitation, and screening for complications.

https://www.cdc.gov/pictureofamerica

# PRIMARY PREVENTION

- Observed benefit counterweighed by risk of complications (primarily bleeding)
- For anti-platelets, no convincing evidence of role in primary prevention
- Most recent statement from CCS is from 2011 pocket guide

## Primary Prevention




## Key Considerations: APT for Primary Prevention

| DO | DON'T |
|---|---|
| • Consider ASA only where there is clear evidence of high risk:<br>  • Asymptomatic carotid stenosis.<br>  • Asymptomatic coronary atherosclerosis.<br>  • Reduced ABI.<br>  • End-stage renal disease. | • Use APT for **primary prevention**. |

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# PRIMARY PREVENTION – More Recent Data

## ASCEND Trial

**Eligibility**: Age ≥ 40 years, any DIABETES and no baseline cardiovascular disease
**Participants**: 15,480 UK patients
**Factorial randomization**: Aspirin 100 mg daily vs placebo (& to omega-3 fatty acid supplements vs placebo)
**Follow-up**: Mean 7.4 years, >99% complete for morbidity and mortality
Adherence: Average difference in anti-platelet use between groups 69%

ORIGINAL ARTICLE

Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus

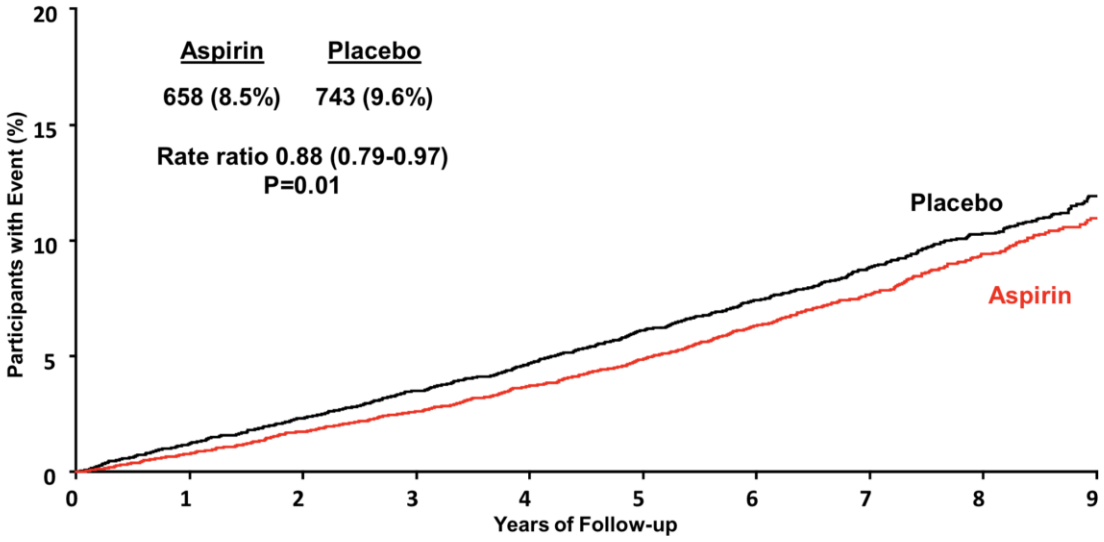
The ASCEND Study Collaborative Group*

N Engl J Med 2018; 379:1529-1539

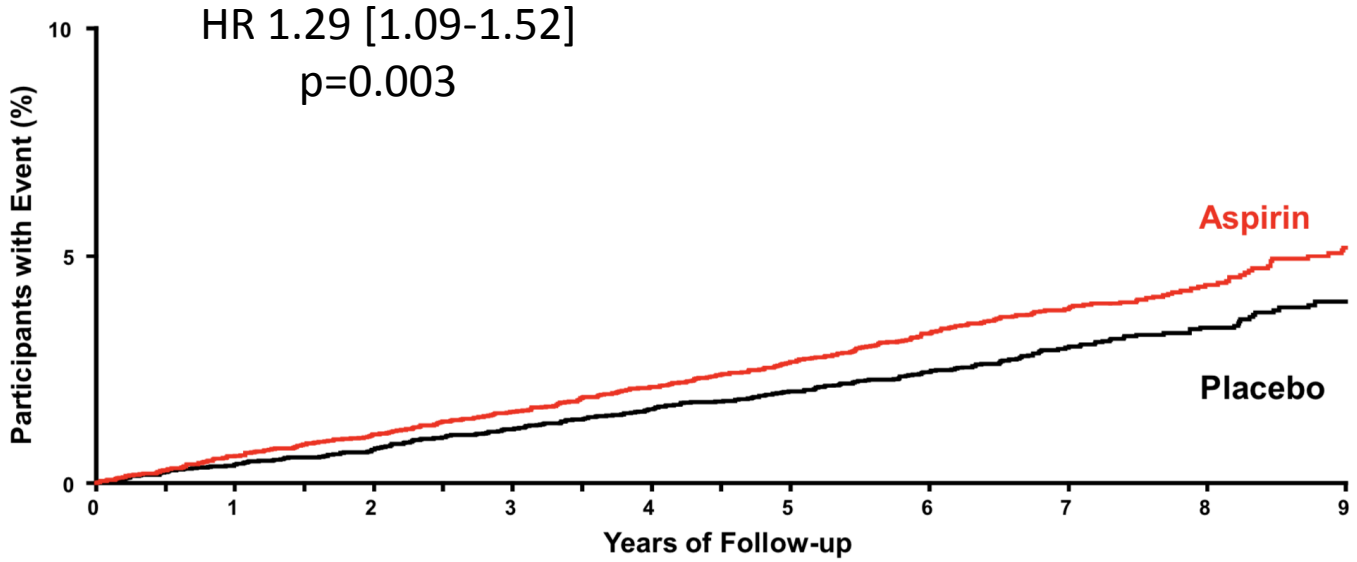
| Characteristic | Aspirin | Placebo |
|---|---|---|
| Age, years | 63 | 63 |
| Male | 63% | 63% |
| Type 2 diabetes | 94% | 94% |
| Diabetes duration, median years | 7 | 7 |
| Hypertension | 62% | 62% |
| Statin use | 76% | 75% |
| Body Mass Index, kg/m$^2$ | 31 | 31 |
| Glycated haemoglobin, mmol/mol | 55 (7.2%) | 55 (7.2%) |

# ASCEND Trial

Efficacy – Effect on SVE




Safety – Rates of Major Bleeding



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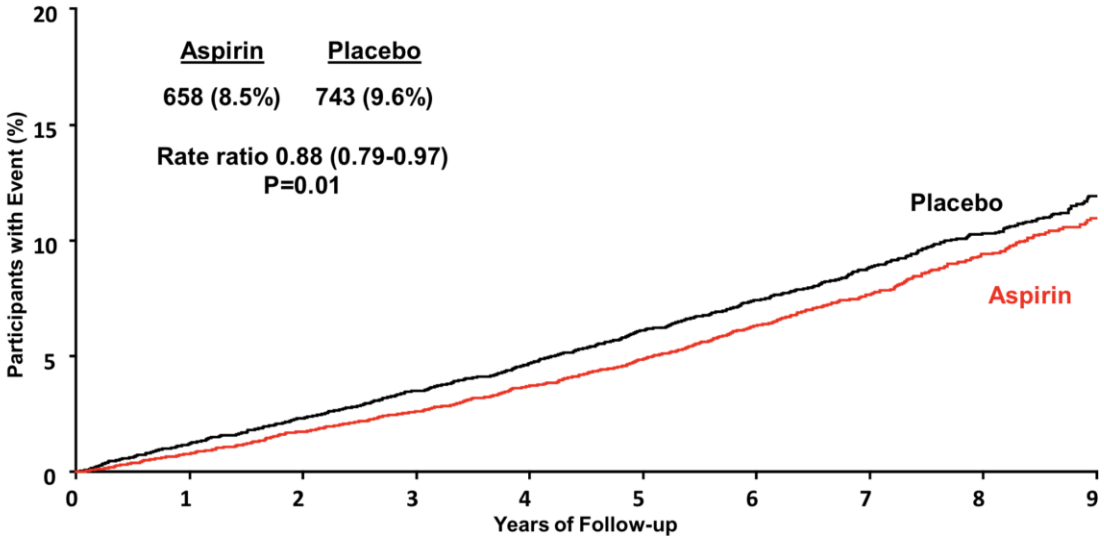


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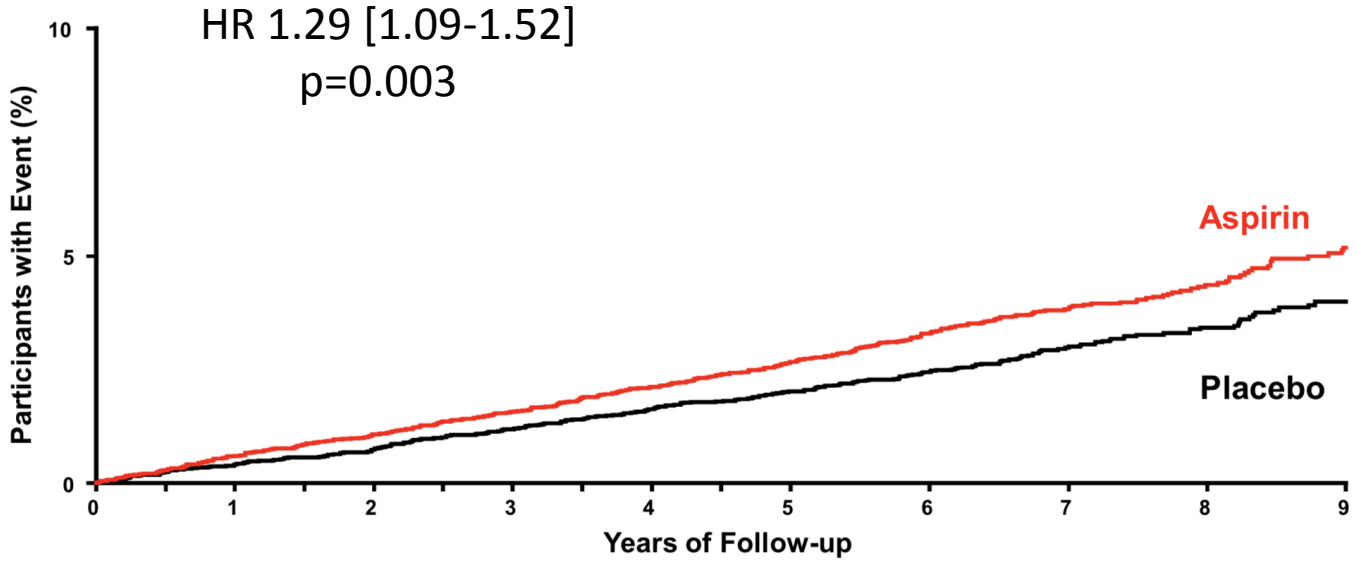
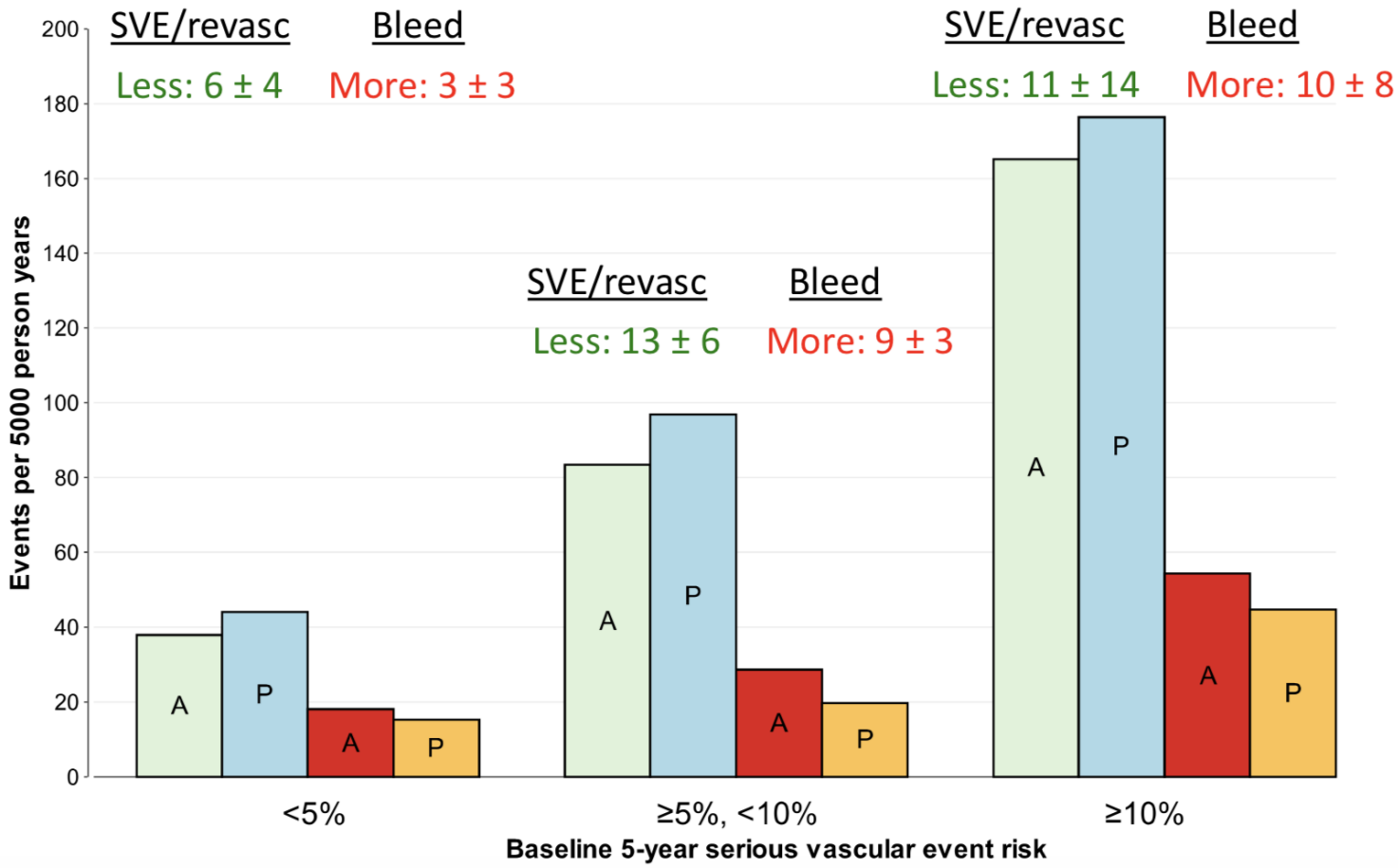


# ASCEND Trial - ?higher risk patients will benefit?



## SECONDARY PREVENTION

- Post ACS, large body of evidence regarding use of anti-platelet therapy
- Aspirin for all plus P2Y12 inhibitor
  - Clopidogrel
  - Prasugrel
  - Ticagrelor

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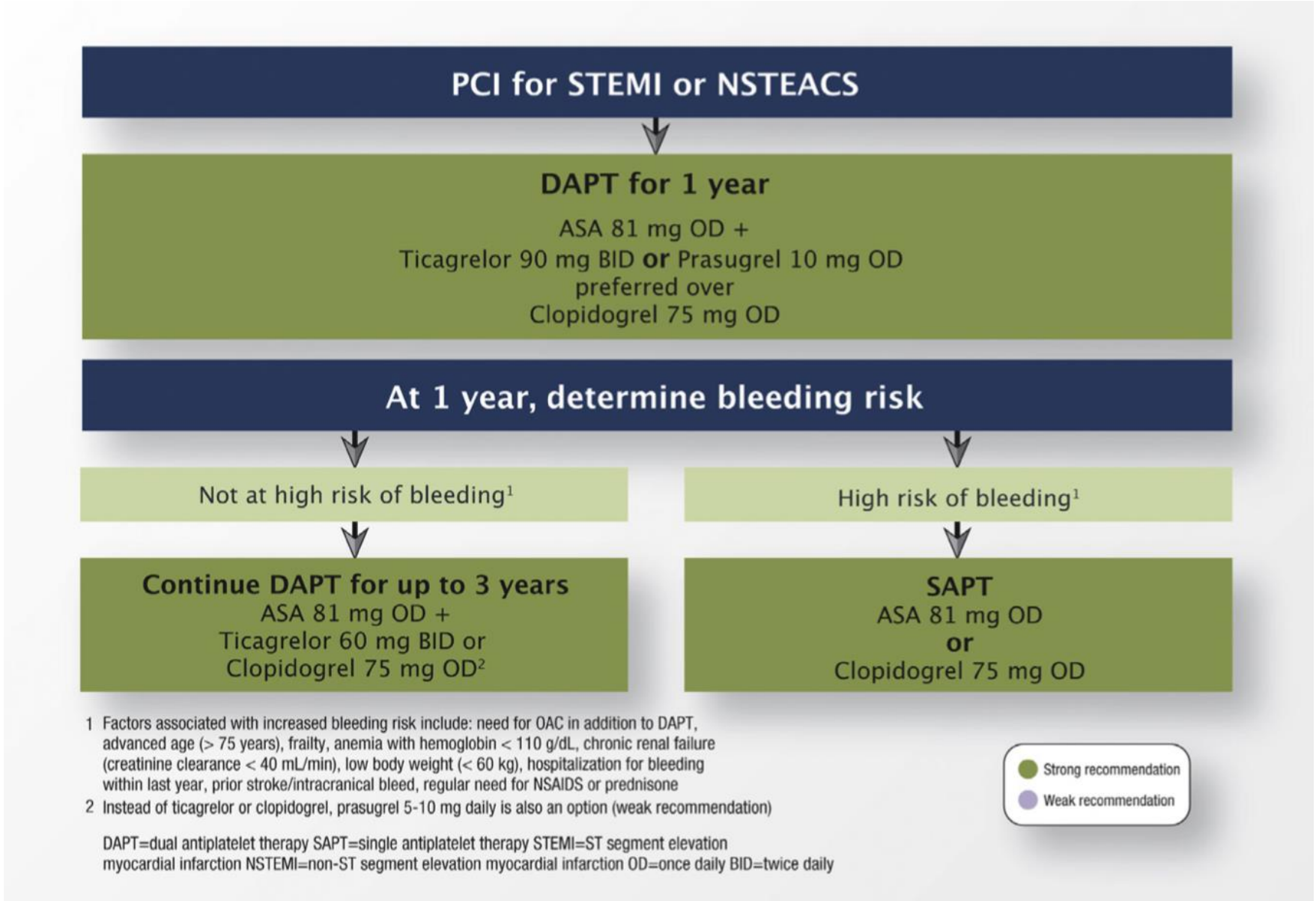
# 2018 CCS Guidelines: STEMI/ NSTEACS




Can. Jour. Cardiol. 2018. 34:214-233

# Ticagrelor/Prasugrel > Clopidogrel

- Preference for these agents stems from TRITON-TIMI 38 and PLATO trials
- Shown to be more effective than clopidogrel WRT combined primary end-point (MI, CVA, death)
  - Marked benefit in rates of stent thrombosis
  - Similar benefit with RRR approx. 20%
  - Excess bleeding with more potent agents
- CCS Guidelines:
  - “These recommendations place greater emphasis on reduction of major CV events and stent thrombosis vs an increase in bleeding complications.”

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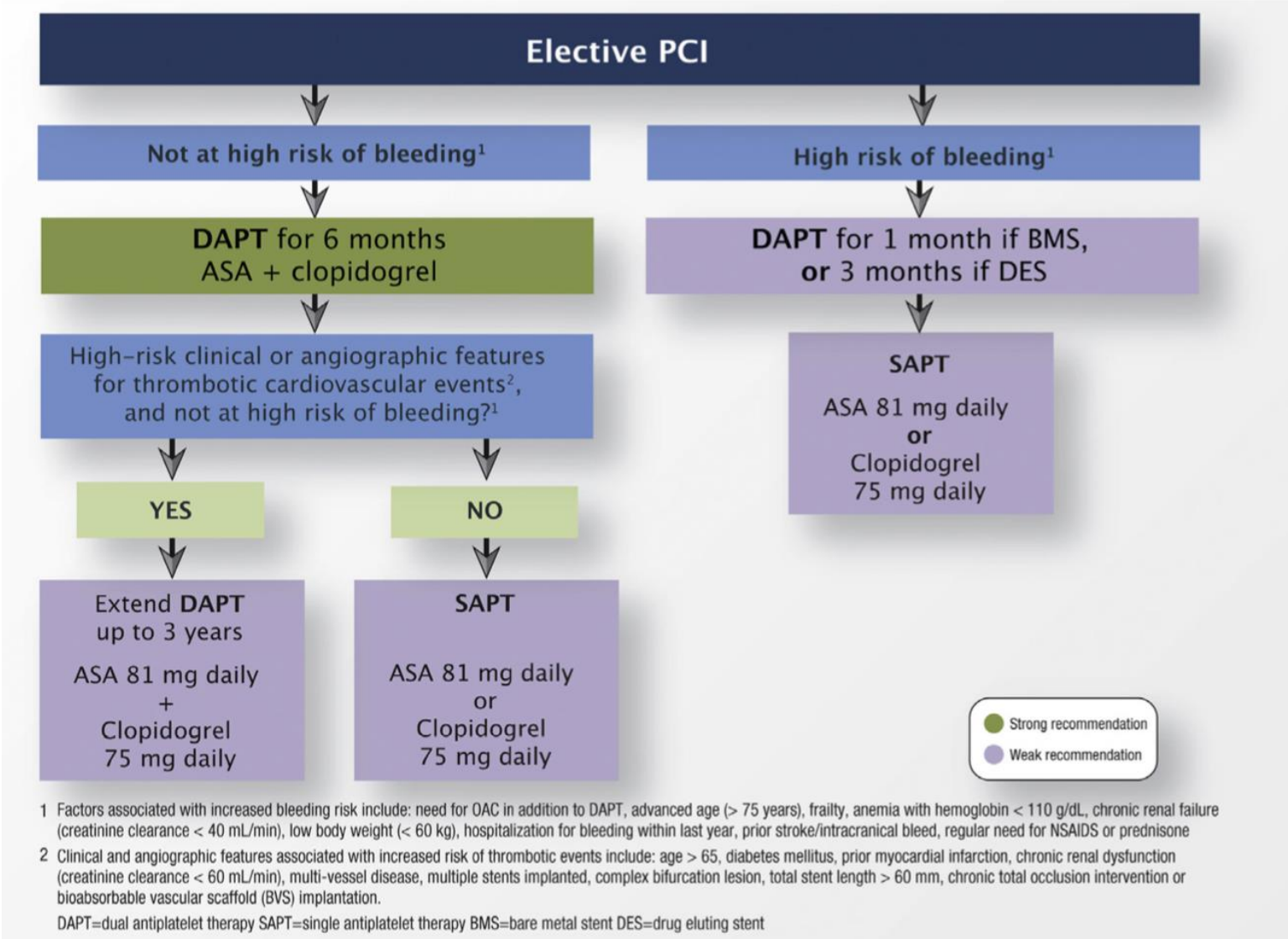
# 2018 CCS Guidelines: Elective PCI

- Reflect latest generation of drug eluting stents
  - Thinner struts
  - Biodegradable/ 'inert' polymer
- Awareness of lower ischemic event risk



# Is Ticagrelor the same as Prasugrel?

- RRR in trials comparing these agents against clopidogrel were similar (approx. 20% for MACE)
- In TRITON-TIMI 38, signals seen in certain subgroups with Prasugrel
  - Low body weight (<60kg) – No benefit
  - Age >75 yrs – No benefit
  - Prior CVA/TIA – evidence of harm
- TRITON-TIMI 38 – treatment was started after coronary anatomy was known (i.e. after angiography)
  - Very US-centric practice
  - Not the case in Canada and Europe (treatment given before anatomy known)
- CCS guidelines reflected these issues with Ticagrelor favoured over prasugrel in majority of cases

ORIGINAL ARTICLE

# Ticagrelor or Prasugrel in Patients with Acute Coronary Syndromes

- ISAR-REACT5 study
- Investigator initiated study comparing Ticagrelor with Prasugrel in ACS patients
- 4018 patients randomized (Germany/ Italy)
- End-point
  - Primary – Composite of death/MI/ stroke at 1 year
  - Secondary – Bleeding safety endpoint

N Engl J Med 2019; 381:1524-1534

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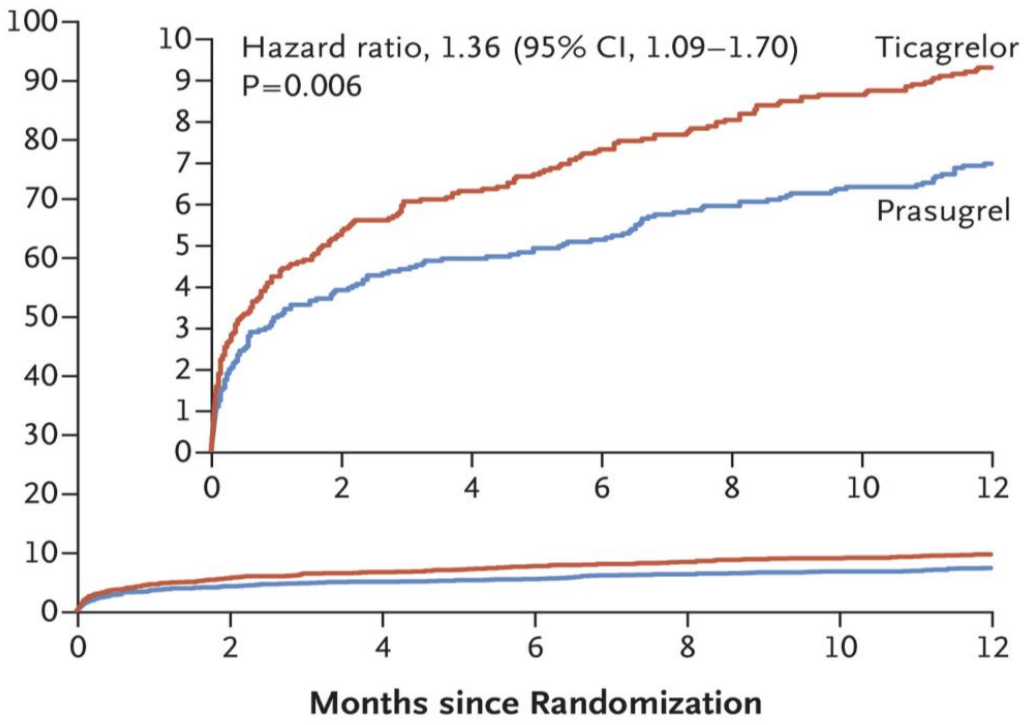
# Results

## Efficacy

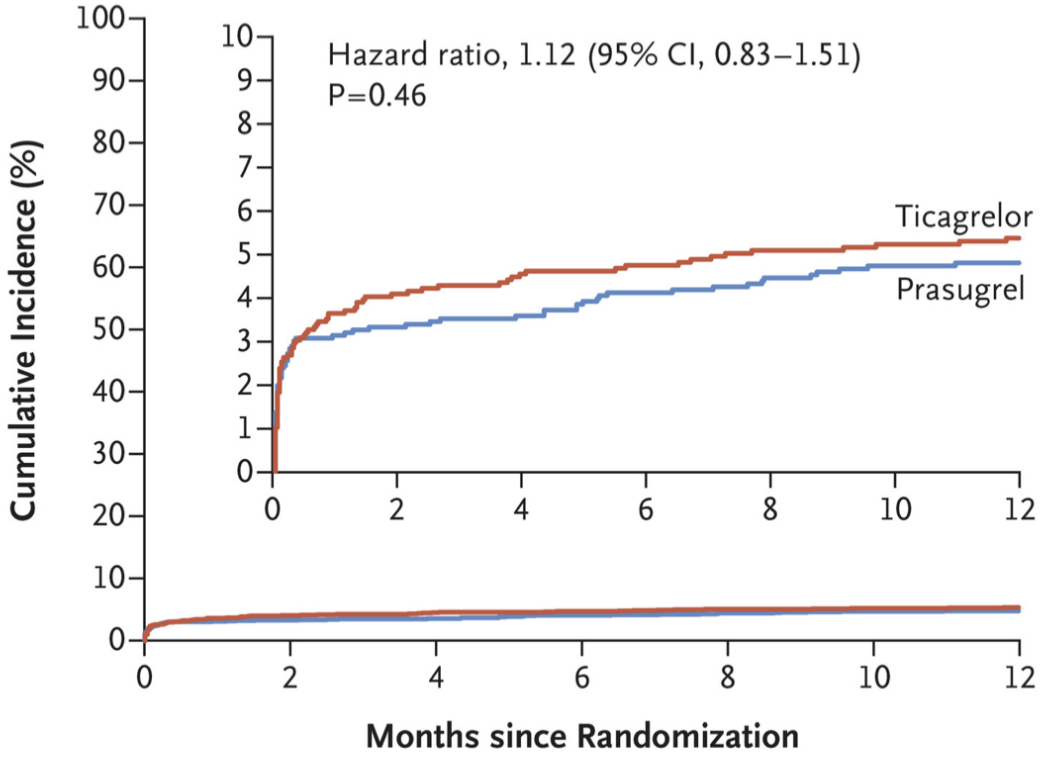
All-cause mortality, MI, CVA




| No. at Risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Ticagrelor | 2012 | 1877 | 1857 | 1835 | 1815 | 1801 | 1722 |
| Prasugrel | 2006 | 1892 | 1877 | 1862 | 1839 | 1829 | 1803 |

## Safety

Bleeding




| No. at Risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Ticagrelor | 1989 | 1441 | 1399 | 1356 | 1319 | 1296 | 1266 |
| Prasugrel | 1773 | 1465 | 1427 | 1397 | 1357 | 1333 | 1307 |

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# I'm Glad that the Concept of DAPT is Sacred  Or is it in its TWILIGHT?

## Ticagrelor with or without Aspirin in High-Risk Patients after PCI

Roxana Mehran, M.D., Usman Baber, M.D., Samin K. Sharma, M.D., David J. Cohen, M.D., Dominick J. Angiolillo, M.D., Ph.D., Carlo Briguori, M.D., Ph.D., Jin Y. Cha, B.S., Timothy Collier, M.Sc., George Dangas, M.D., Ph.D., Dariusz Dudek, M.D., Ph.D., Vladimír Džavík, M.D., Javier Escaned, M.D., Ph.D., et al.

- Post PCI – treated with ASA/Ticagrelor for 3/12
- At 3/12, if no ischemic/bleeding endpoints, randomized:
  - Ticagrelor + placebo, vs
  - Ticagrelor + ASA
- End-point:
  - Primary - BARC type 2, 3 or 5 bleeding (actionable, Hgb drop or fatal)
  - Secondary - All-cause mortality, MI, CVA

N Engl J Med 2019; 381:2032-2042

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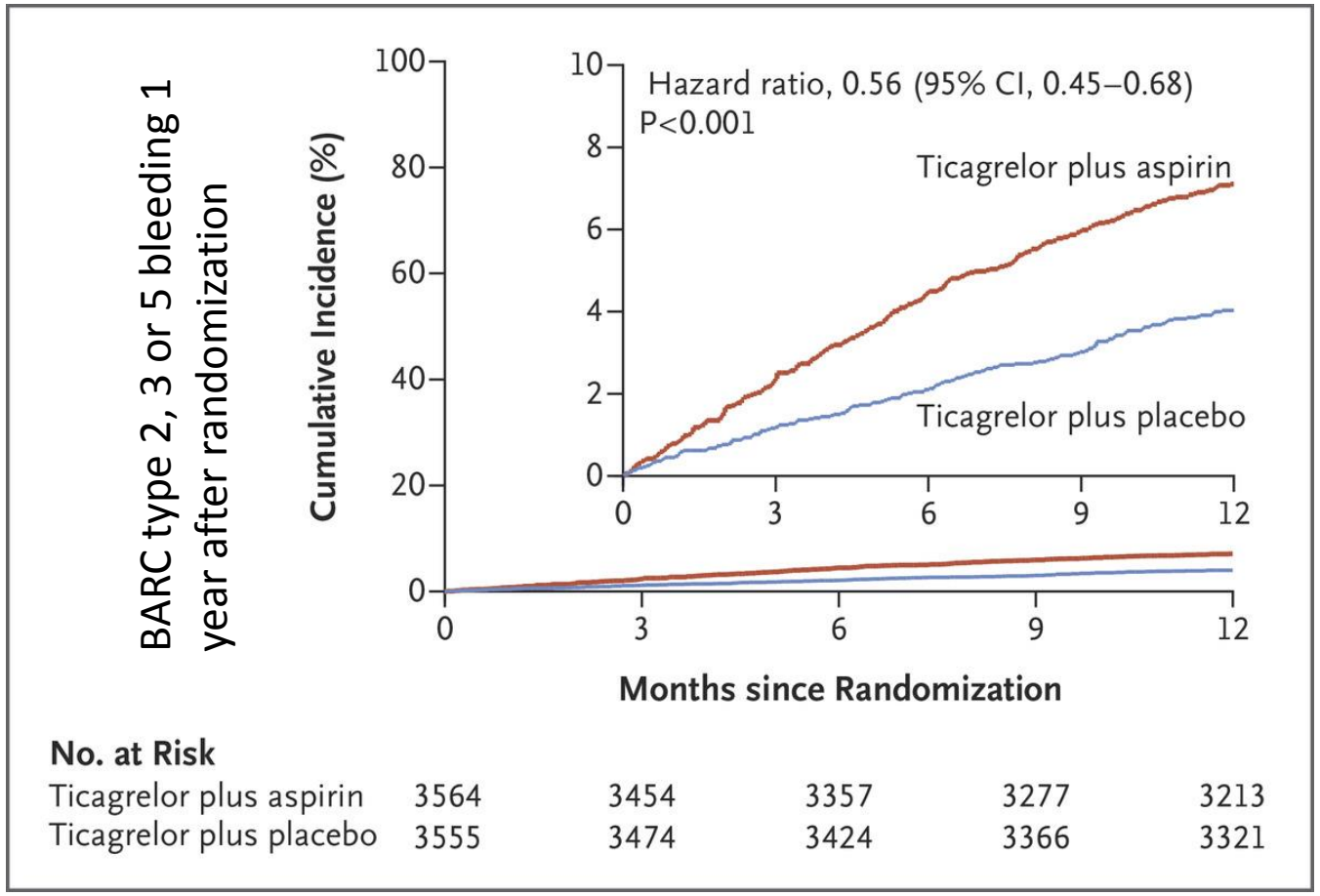


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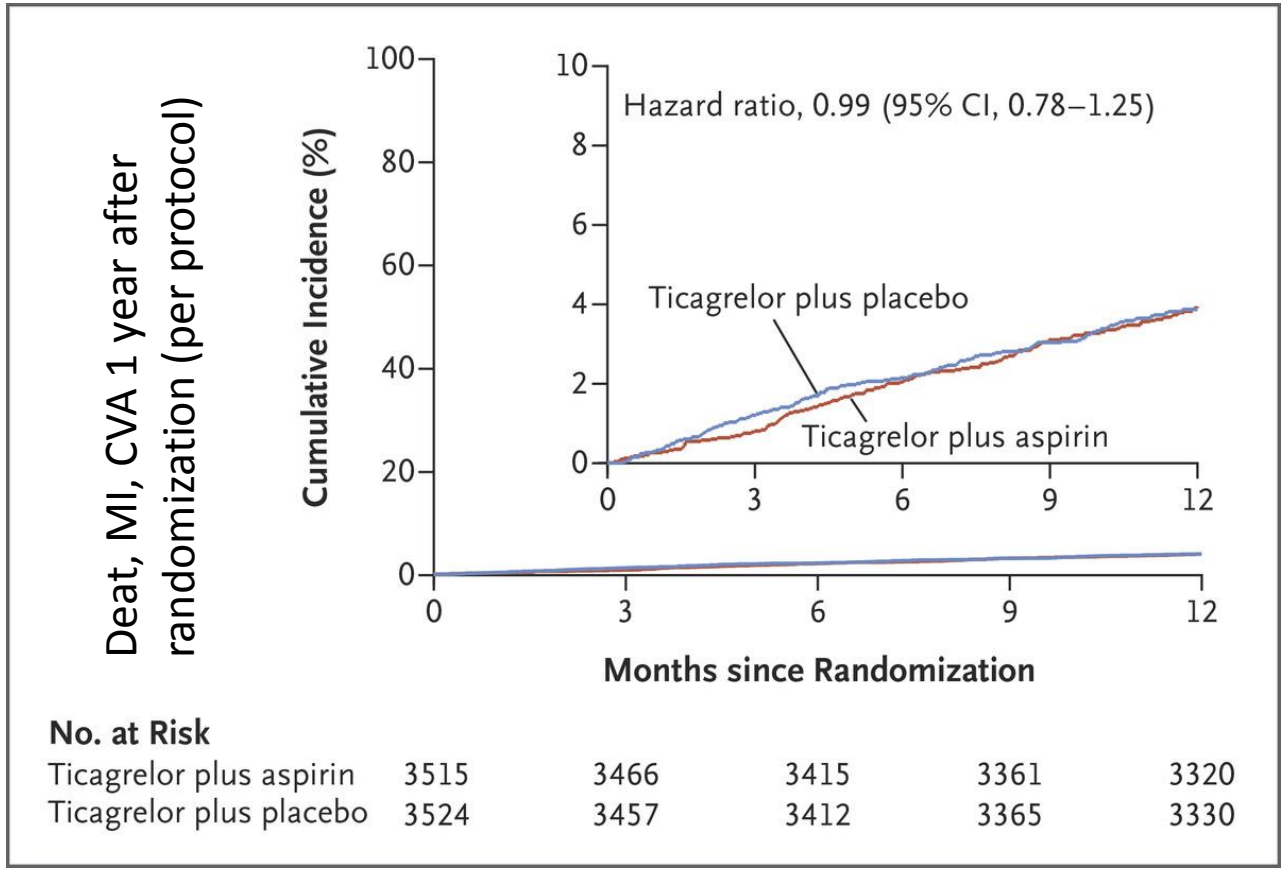


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## Enough about Anti-platelets; what about anti-thrombotics?

## ACS – APPRAISE-2 & ATLAS ACS2

ORIGINAL ARTICLE

# Rivaroxaban in Patients with a Recent Acute Coronary Syndrome

Jessica L. Mega, M.D., M.P.H., Eugene Braunwald, M.D., Stephen D. Wiviott, M.D., Jean-Pierre Bassand, M.D., Deepak L. Bhatt, M.D., M.P.H., Christoph Bode, M.D., Paul Burton, M.D., Ph.D., Marc Cohen, M.D., Nancy Cook-Bruns, M.D., Keith A.A. Fox, M.B., Ch.B., Shinya Goto, M.D., Sabina A. Murphy, M.P.H., et al., for the ATLAS ACS 2–TIMI 51 Investigators*

N Engl J Med 2012; 366:9-19

ORIGINAL ARTICLE

# Apixaban with Antiplatelet Therapy after Acute Coronary Syndrome

John H. Alexander, M.D., M.H.S., Renato D. Lopes, M.D., Ph.D., Stefan James, M.D., Ph.D., Rakhi Kilaru, M.S., Yaohua He, M.D., Ph.D., Puneet Mohan, M.D., Ph.D., Deepak L. Bhatt, M.D., M.P.H., Shaun Goodman, M.D., Freek W. Verheugt, M.D., Ph.D., Marcus Flather, M.D., Kurt Huber, M.D., Danny Liaw, M.D., Ph.D., et al., for the APPRAISE-2 Investigators*

N Engl J Med 2011; 365:699-708

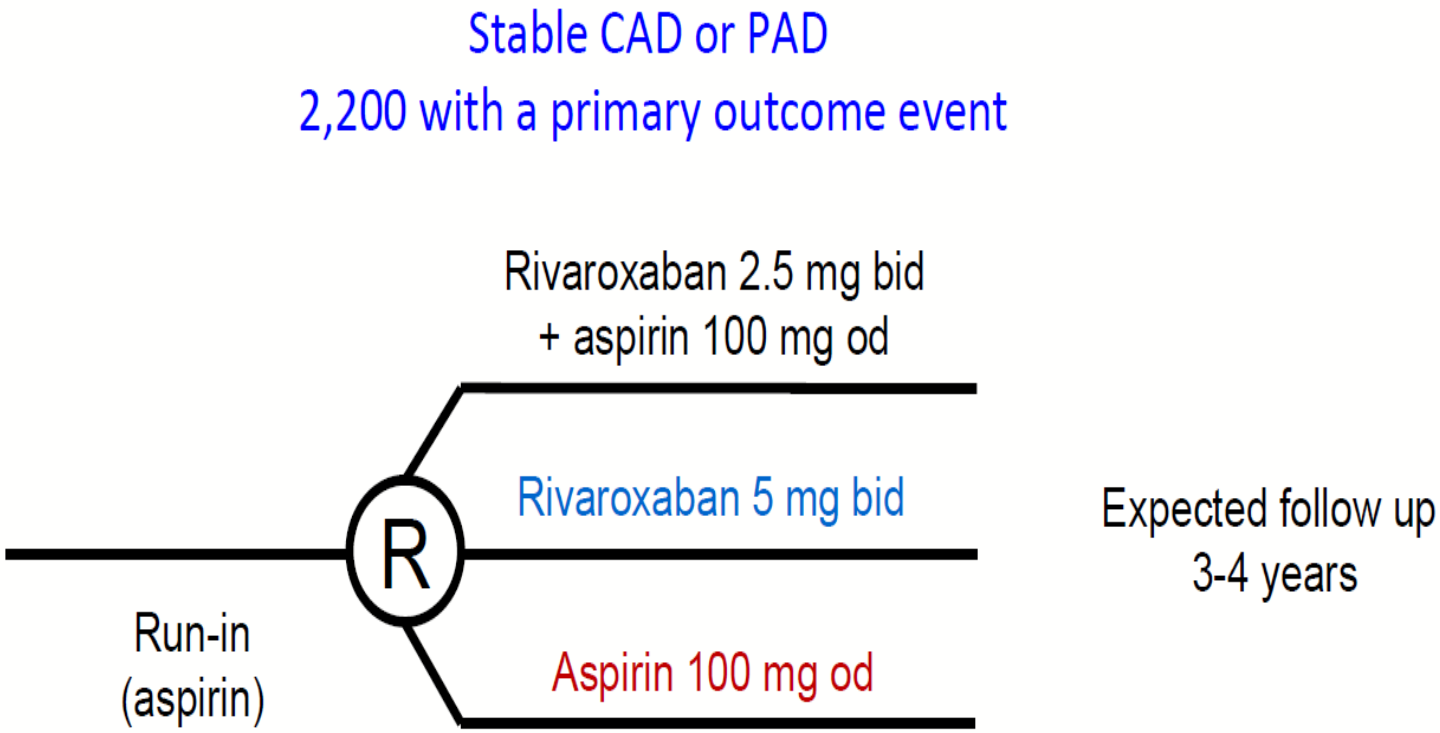
# Anti-thrombotic Post ACS

- **ATLAS ACS2 – >15,000patients. Rivaroxaban reduced rate of MACE but at expense of major bleeds (inc. IC hemorrhage). Bleeding worse with 5mg bid dose.**

- **APPRAISE2 – terminated prematurely after 7,000 patients. No reduction in ischemic events**

# Anti-thrombotics-Secondary Prevention with Rivaroxaban

## COMPASS Trial Design




Adapted from: Eikelboom JW, et al. N Engl J Med 2017;377:1319-30

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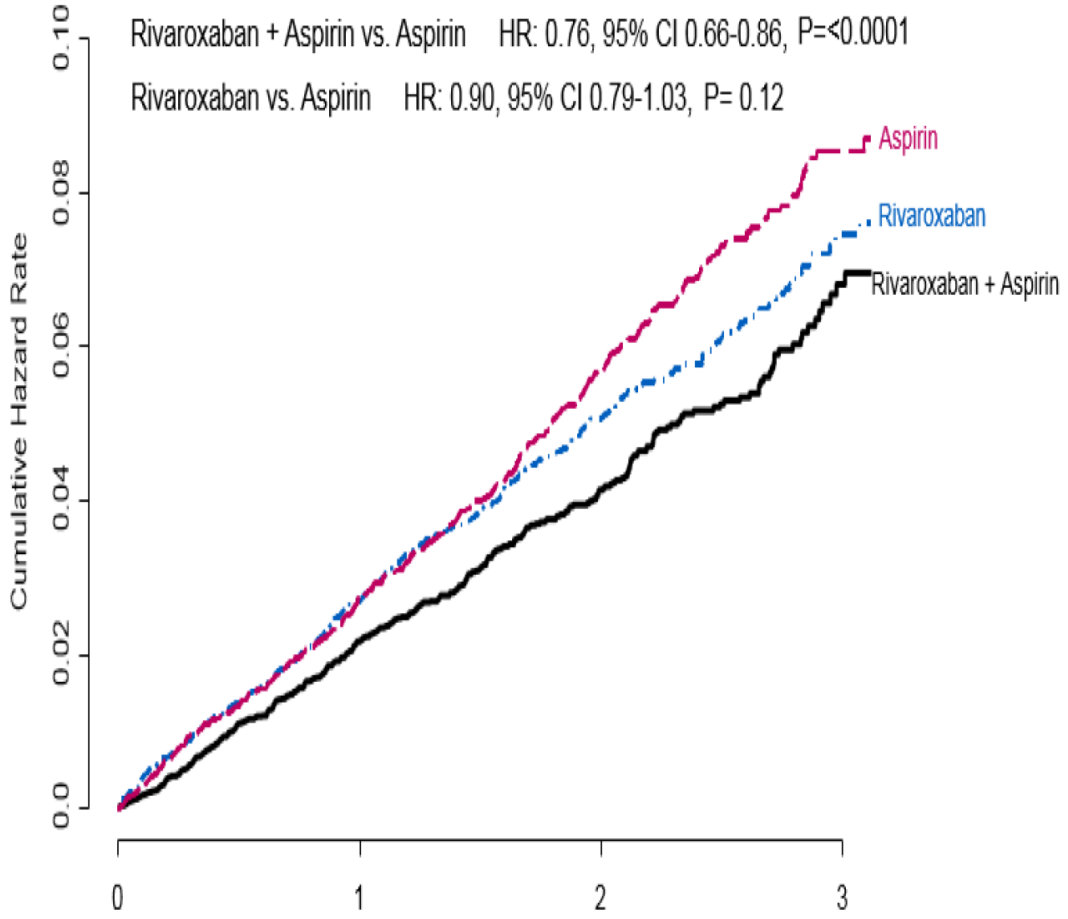
# COMPASS Trial: Results




| Outcome | R + A N=9,152 | A N=9,126 | Rivaroxaban + Aspirin vs. Aspirin | |
|---|---|---|---|---|
| | N (%) | N (%) | HR (95% CI) | p |
| CV death | 160 (1.7%) | 203 (2.2%) | 0.78 (0.64-0.96) | 0.02 |
| Stroke | 83 (0.9%) | 142 (1.6%) | 0.58 (0.44-0.76) | <0.0001 |
| MI | 178 (1.9%) | 205 (2.2%) | 0.86 (0.70-1.05) | 0.14 |
| CHD death, IS, MI, ALI | 329 (3.6%) | 450 (4.9%) | 0.72 (0.63-0.83) | <0.0001 |
| CV death, IS, MI, ALI | 389 (4.3%) | 516 (5.7%) | 0.74 (0.65-0.85) | <0.0001 |
| Mortality | 313 (3.4%) | 378 (4.1%) | 0.82 (0.71-0.96) | 0.01 |

* pre-specified threshold P=0.0025

Major bleeding increased: HR 1.70 (95% CI 1.40-2.05) p<0.001

Eikelboom et al. NEJM 2017

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# Chronic Therapy – Personal biases/thoughts

| | $P2Y_{12}$ receptor inhibitor | Rivaroxaban |
|---|---|---|
| Polyvascular disease | | ✓ |
| Recurrent MI/PCI | ✓ | |
| Complex PCI | ✓ | |
| Prior stent thrombosis | ✓ | |
| Time of MI | | |
| 1-3 yrs ago | ? ✓ | |
| >3 yrs ago | | ? ✓ |

**SUMMARY**

- As in most fields of cardiology, there is a large body of evidence regarding the use of anti-platelets and anti-thrombotics
- Currently no evidence for net benefit with ‘true’ primary prevention for anti-platelets
- DAPT has been established as standard of care over the last 2 decades
    - Recent TWILIGHT study has questioned this
    - ISAR REACT 5 may renew interest in Prasugrel
- Concomitant use of anti-thrombotics is beneficial:
    - ACS – not firmly established (excess bleding)
    - Chronic – clear benefit
- As with any effective anti-platelet/anti-thrombotic, the cost is in excess bleeding and must be weighed up individually

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**THANK YOU**

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