Optimal DAPT Strategies: Lessons Learned, Global Leaders, TWILIGHT, and More

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New York, NY, USA
### Disclosures

<table>
<thead>
<tr>
<th>Affiliation/Financial Relationship</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consultant/ Exec committee/Advisory board/personal fees</td>
<td>Abbott Laboratories, Boston Scientific, Medscape, Siemens Medical Solutions, Phillips (Spectranetics), PLx Pharma, Roivant Sciences Inc, Volcano Corporation, Sanofi, Janssen,</td>
</tr>
<tr>
<td>Research Funding to Institution</td>
<td>Abbott Laboratories, AstraZeneca, Bayer, Beth Israel Deaconess, BMS, CSL Behring, DSI, Medtronic, Boston Scientific, Novartis, OrbusNeich</td>
</tr>
<tr>
<td>Equity, &lt;1%</td>
<td>Claret Medical, Elixir Medical</td>
</tr>
<tr>
<td>DSMB membership paid to the institution</td>
<td>Watermark Research Partners</td>
</tr>
</tbody>
</table>
Some History

- Triple Therapy and Dual Therapy for AF/PCI
- P2Y12 inhibition alone after PCI
A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE)

CAPRIE Steering Committee*

- N = 19,185
- Clopidogrel versus aspirin in atherosclerotic vascular disease
- Stroke, MI or vascular death: RR 0.91; p = 0.43

<table>
<thead>
<tr>
<th>Adverse experience</th>
<th>Clopidogrel</th>
<th>Aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>578 (6.02%)</td>
<td>442 (4.61%)*</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>428 (4.46%)</td>
<td>322 (3.36%)*</td>
</tr>
<tr>
<td>Indigestion/nausea/vomiting</td>
<td>1441 (15.01%)</td>
<td>1686 (17.59%)*</td>
</tr>
<tr>
<td>Any bleeding disorder</td>
<td>890 (9.27%)</td>
<td>890 (9.28%)</td>
</tr>
<tr>
<td>Intracranial haemorrhage</td>
<td>34 (0.35%)</td>
<td>47 (0.49%)</td>
</tr>
<tr>
<td>Gastrointestinal haemorrhage</td>
<td>191 (1.99%)</td>
<td>255 (2.66%)*</td>
</tr>
<tr>
<td>Abnormal liver function</td>
<td>285 (2.97%)</td>
<td>302 (3.15%)*</td>
</tr>
</tbody>
</table>

Statistically significant: * p < 0.05

Lancet 1996
CURE Trial

- 12,562 patients with NSTE-ACS
- Randomized to clopidogrel (300 mg loading dose and 75 mg daily maintenance dose) or placebo; background ASA
- Treatment at the discretion of the treating physician

Yusuf et al., NEJM 2001
PCI-CURE Study: CV Death or MI from randomization

- Placebo + aspirin (n = 1345): 12.6%
- Clopidogrel + aspirin (n = 1313): 8.8%

31% reduction in relative risk

Cumulative hazard rate vs. Days of follow-up

Median time to PCI

$P = 0.002$

MI = myocardial infarction; CV = cardiovascular
Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial

**Efficacy (ischemic events)**

- **Placebo and clopidogrel**
  - Patients at risk: 3797, 3576, 3440, 3321, 3229, 3130, 2441
  - Cumulative event rate (%): 0, 4, 8, 12, 16, 20

- **Aspirin and clopidogrel**
  - Patients at risk: 3802, 3576, 3439, 3326, 3200, 3119, 2446
  - Cumulative event rate (%): 0, 4, 8, 12, 16, 20

**Safety (ICH)**

- **Placebo and clopidogrel**
  - Patients at risk: 3724, 3691, 3643, 3601, 3552, 3508, 2756
  - Cumulative event rate (%): 0, 1, 2, 3, 4

- **Aspirin and clopidogrel**
  - Patients at risk: 3781, 3576, 3686, 3638, 3582, 3544, 2823
  - Cumulative event rate (%): 0, 1, 2, 3, 4

**p-values**: 0.244 (Efficacy), 0.029 (Safety)
Some History

- **Triple Therapy and Dual Therapy for AF/PCI**

- P2Y12 inhibition alone after PCI
Atrial Fibrillation and PCI: Key Concepts

Stent thrombosis and coronary events
↓
High shear stress platelet-rich thrombi
↓
Antiplatelet therapy

Stroke, TIA and systemic embolism
↓
Low shear stress, less platelet-dependent thrombi
↓
Anticoagulation therapy

**The What is the Optimal antiplatelet and anticoagulant therapy in patients with oral anticoagulation and coronary Stenting Trial (WOEST)**

**Design**

- **DESIGN:** randomized, placebo-controlled, open-label, multi-center trial
- **OBJECTIVE:** to compare the safety and efficacy of clopidogrel alone with clopidogrel + ASA in patients taking OAC therapy and undergoing PCI

573 patients treated with OAC and undergoing PCI from November 2008 to November 2011 at 15 centers in Belgium and Netherlands

ACS ~ 25% in both groups
DES used in 65% in both groups

573 patients treated with OAC and undergoing PCI from November 2008 to November 2011 at 15 centers in Belgium and Netherlands

ACS ~ 25% in both groups
DES used in 65% in both groups

**Warfarin + Clopidogrel**
*(The double-therapy group)*
N = 284

**Warfarin + ASA + Clopidogrel**
*(The triple-therapy group)*
N = 289

**F/U:** median 365 days

**1° endpoint:** any bleeding episode during 1 year
**2° endpoint:** death, MI, stroke, TVR, and ST

WOEST Primary Endpoint:
TIMI Major or Minor or Minimal Bleeding

Dewilde et al – Lancet 2013
Apixaban Versus Warfarin in Patients with AF and ACS or PCI: The AUGUSTUS Trial

**Primary outcome:** major/clinically relevant bleeding (through 6 months)

**Secondary objective:** Death, MI, stroke, stent thrombosis

**Randomize**

\[ n = 4,600 \]

**Patients**

**Inclusion**
- AF (prior, persistent, or >6 hrs duration)
- Physician decision that oral anticoag is indicated
- ACS or PCI with planned P2Y12 inhibitor for 6 months

**Exclusion**
- Contraindication to DAPT
- Other reason for warfarin (prosthetic valve, mod/sev MS)

**Apixaban**
- P2Y12 inhibitor for all patients x 6 months
- Aspirin for all on the day of ACS or PCI
- Aspirin versus placebo after randomization

**Warfarin**
- ASA
- placebo

**Primary outcome:** major/clinically relevant bleeding (through 6 months)

**Secondary objective:** Death, MI, stroke, stent thrombosis
Stent thrombosis rates were lower with ASA vs. placebo (0.5% vs. 0.9%)

MI rates were lower with ASA vs. placebo (2.9% vs. 3.6%)

Lopes et al. NEJM 2019
AF/PCI: The North American Perspective – 2018 Update

Antithrombotic Therapy in Patients With Atrial Fibrillation Treated With Oral Anticoagulation Undergoing Percutaneous Coronary Intervention
A North American Perspective–2018 Update

Dominick J. Angiolillo, MD, PhD, Shaun G. Goodman, MD, Deepak L. Bhatt, MD, MPH, John W. Eikelboom, MD, Matthew J. Price, MD, David J. Moliterno, MD, Christopher P. Cannon, MD, Jean-Francois Tanguay, MD, Christopher B. Granger, MD, Laura Mauri, MD, David R. Holmes, MD, C. Michael Gibson, MD, David P. Faxon, MD

OAC: prefer a NOAC over VKA if no contraindications
SAPT: prefer a P2Y12 inhibitor over aspirin
Clopidogrel is the P2Y12 inhibitor of choice; ticagrelor may be considered in patients at high ischemic/thrombotic and low bleeding risks, avoid prasugrel
Consider SAPT in addition to OAC after >12 mo, only in select patients at high ischemic/thrombotic and low bleeding risks

Some History

Triple Therapy and Dual Therapy for AF/PCI

P2Y12 inhibition alone after PCI
Increasing importance of bleeding

**ACUITY: Influence of Major Bleeding and MI in the First 30 Days on Risk of Death Over 1-Year**

Of 13,819 enrolled patients, 524 (3.8%) died within 1 year

Cox model adjusted for 36 baseline predictors, with MI and major bleeding (non-CABG) as time-updated covariates

<table>
<thead>
<tr>
<th>Event Description</th>
<th>HR ± 95% CI</th>
<th>HR (95% CI)</th>
<th>P-value</th>
<th>Attributable deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td></td>
<td>2.51 (1.95-3.25)</td>
<td>&lt;0.0001</td>
<td>51.5*</td>
</tr>
<tr>
<td>Major bleeding without or before transfusion</td>
<td></td>
<td>2.00 (1.30-3.06)</td>
<td>&lt;0.0001</td>
<td>66.5**</td>
</tr>
<tr>
<td>Major bleeding after transfusion</td>
<td></td>
<td>3.93 (2.95-5.24)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

*Mehran RM et al. EHJ 2009;30:1457-66*
Increasing importance of bleeding

Post discharge bleeding increases mortality significantly

Data from ADAPT-DES study (2-years follow up)

<table>
<thead>
<tr>
<th>Variables</th>
<th>HR [95% CI]</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-discharge bleeding*</td>
<td>3.91 [2.90, 5.27]</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Myocardial infarction*</td>
<td>3.30 [2.35, 4.65]</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Current smoker</td>
<td>1.64 [1.21, 2.22]</td>
<td>0.001</td>
</tr>
<tr>
<td>Age, years</td>
<td>1.46 [1.26, 1.69]</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Male</td>
<td>1.46 [1.11, 1.92]</td>
<td>0.007</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.45 [1.15, 1.84]</td>
<td>0.002</td>
</tr>
<tr>
<td>Previous MI</td>
<td>1.44 [1.13, 1.84]</td>
<td>0.003</td>
</tr>
<tr>
<td>STEMI or NSTEMI</td>
<td>1.40 [1.08, 1.80]</td>
<td>0.01</td>
</tr>
<tr>
<td>VerifyNow PRU &gt;208</td>
<td>1.24 [0.98, 1.57]</td>
<td>0.08</td>
</tr>
<tr>
<td>Creatinine clearance (per 10 unit decrease)</td>
<td>1.07 [1.03, 1.12]</td>
<td>0.002</td>
</tr>
<tr>
<td>Baseline WBC (10^3/mL)</td>
<td>1.03 [1.01, 1.04]</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Baseline Hb (g/dL)</td>
<td>0.84 [0.77, 0.91]</td>
<td>&lt;0.00001</td>
</tr>
</tbody>
</table>

Généreux P. et al. J Am Coll Cardiol. 2015 Sep 1;66(9):1036-45
TEN YEARS SINCE PLATO!

6–12-month exposure

**Clopidogrel**
- If pretreated, no additional loading dose;
- if naive, standard 300 mg loading dose, then 75 mg qd maintenance;
- (additional 300 mg allowed pre-PCI)

**Ticagrelor**
- 180 mg loading dose, then 90 mg BID maintenance;
- (additional 90 mg pre-PCI)

NSTEMI-ACS (moderate-to-high risk), STEMI (if primary PCI)
- Clopidogrel-treated or -naive;
- randomized within 24 hours of index event
  - (N = 18,624)

Primary endpoint: CV death + MI + Stroke

Primary safety endpoint: Total major bleeding
PLATO: Primary Endpoints

Primary Efficacy: CV death + MI + Stroke

- Clopidogrel: 11.7%
- Ticagrelor: 9.8%

RRR~16%

HR 0.84 (95% CI 0.77–0.92), P=.0003

No. at risk

<table>
<thead>
<tr>
<th>Drug</th>
<th>Days after Randomisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ticagrelor</td>
<td>9,333 8,628 8,460 8,219 6,743 5,161 4,147</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>9,291 8,521 8,362 8,124 6,650 5,096 4,047</td>
</tr>
</tbody>
</table>

*Composite of CV death, MI, or stroke

Primary Safety: Major Bleeding

- Ticagrelor: 11.6%
- Clopidogrel: 11.2%

HR 1.04, P=.434(NS)

No. at risk

<table>
<thead>
<tr>
<th>Drug</th>
<th>Days from first IP dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ticagrelor</td>
<td>9,235 7,246 6,826 6,545 5,129 3,783 3,433</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>9,186 7,305 6,930 6,670 5,209 3,841 3,479</td>
</tr>
</tbody>
</table>

*Major bleed as defined by PLATO criteria
Impact of PLATO

Change in Guidelines – Ticagrelor is preferred in ACS patients
Registry data shows that use of Ticagrelor has increased drastically

However, questions remained...

- Low proportion of US enrollment
- Issue of Aspirin Interaction
- Lack of Benefit in the US
Success of Low Dose Aspirin in PLATO

In PLATO, the ticagrelor-to-clopidogrel hazard ratio (HR) for the primary EP was:

- Low-dose aspirin: 0.79 (95% CI, 0.71-0.88)
- High-dose aspirin: 1.45 (95% CI, 1.01-2.09)

<table>
<thead>
<tr>
<th>Aspirin dosage</th>
<th>US, HR (95% CI)</th>
<th>Non-US (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;300 mg</td>
<td>1.62 (0.99-2.64)</td>
<td>1.23 (0.71-2.14)</td>
</tr>
<tr>
<td>&gt;100 to &lt;300 mg</td>
<td>*</td>
<td>1.00 (0.71-1.42)</td>
</tr>
<tr>
<td>&lt;100 mg</td>
<td>0.73 (0.40-1.33)</td>
<td>0.78 (0.69-0.87)</td>
</tr>
</tbody>
</table>

If less is more, will none be even better?

GLOBAL LEADERS

Primary endpoint: Composite of all-cause mortality or non-fatal new Q-wave MI up to 2 years post randomization

Safety endpoint: Investigator-reported BARC 3 or 5 bleeding up to 2 years

Experimental strategy

ACS + Stable CAD
ASA 75-100 mg/d
Ticagrelor 90 mg bid

Reference strategy

ACS: UA+NSTEMI+STEMI
ASA 75-100 mg/d
Ticagrelor 90 mg bid

Stable CAD
ASA 75-100 mg/d
Clopidogrel 75 mg/d

"All-comers" PCI population
N = 15,991
1:1 Randomisation, open-label design, 130 centers worldwide

•Any type of lesions: Left main, SVG, CTO bifurcation, ISR, etc.
•Unrestricted use of DES (number, length)

Bivalirudin-supported BioMatrix DES by default

Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial

Pascal Vonckx*, Marco Valgimigii*, Peter Jüni*, Christian Hamm, Philippe Gabriel Steg, Dirk Heg, Gerrit Anne van Es, Eugene P McFadden, Yoshinobu Onuma, Cokky van Meijeren, Piy Chichareon, Edouard Benit, Helge Møllmann, Luc Janssens, Maurizio Ferrario, Aris Moschovitis, Aleksander Zurakowski, Marcello Dominici, Robert Jan Van Geuns, Kurt Huber, Ton Slagboom, Patrick W Serruys, Stephan Windecker, on behalf of the GLOBAL LEADERS investigators
GLOBAL LEADERS – A Missed Opportunity?

Primary and secondary outcomes at 24 months (Intention to treat)

<table>
<thead>
<tr>
<th></th>
<th>Experimental group</th>
<th>Reference group</th>
<th>Risk Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of pts.</strong></td>
<td>N=7980</td>
<td>N=7988</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>All-cause mortality or new Q-wave MI</strong></td>
<td>3.81 % (304)</td>
<td>4.37 % (349)</td>
<td>0.87 (0.75-1.01)</td>
<td>0.073</td>
</tr>
<tr>
<td><strong>All-cause mortality</strong></td>
<td>2.81 % (224)</td>
<td>3.17 % (253)</td>
<td>0.88 (0.74-1.06)</td>
<td>0.18</td>
</tr>
<tr>
<td><strong>New Q-wave MI</strong></td>
<td>1.04 % (83)</td>
<td>1.29 % (103)</td>
<td>0.80 (0.60-1.07)</td>
<td>0.14</td>
</tr>
<tr>
<td><strong>BARC 3 or 5 Bleeding</strong></td>
<td>2.04 % (83)</td>
<td>2.12 % (103)</td>
<td>0.97 (0.78-1.20)</td>
<td>0.77</td>
</tr>
<tr>
<td><strong>BARC 5 Bleeding</strong></td>
<td>0.28 % (22)</td>
<td>0.30 % (30)</td>
<td>0.92 (0.52-1.64)</td>
<td>0.78</td>
</tr>
<tr>
<td><strong>BARC 3 Bleeding</strong></td>
<td>1.88 % (115)</td>
<td>1.99 % (130)</td>
<td>0.95 (0.76-1.18)</td>
<td>0.63</td>
</tr>
</tbody>
</table>

Limitations

- Linked to a single stent platform
- No US data; primarily in Europe
- Lack of centralized adjudication; investigator-reported events
- Comparator arm has multiple embedded comparisons
Presented at EuroPCR 2019!

A consensus definition of patients at HBR was developed based on review of available evidence

Represents the first pragmatic approach to a consistent HBR definition in clinical trials evaluating the safety and effectiveness of devices and drug regimens for patients undergoing PCI

Patients are considered to be at HBR if at least 1 major OR 2 minor criteria are met
Primary Objective:
To determine the impact of SAPT (ticagrelor monotherapy) \textit{versus} DAPT (ticagrelor plus aspirin) for 12 months in reducing \textbf{clinically relevant bleeding} (BARC 2, 3 or 5) among high-risk patients who have undergone successful PCI.

Secondary Objective:
To determine the impact of SAPT (ticagrelor monotherapy) \textit{versus} DAPT (ticagrelor plus aspirin) for 12 months on \textbf{major ischemic adverse events} (all-cause death, non-fatal MI or stroke) among high-risk patients who have undergone successful PCI.
Methods

TWILIGHT was a randomized, double-blinded, placebo-controlled trial conducted in 187 sites across 11 countries.

Patients undergoing successful PCI with at least 1 locally-approved DES whom the treating clinician intended to discharge on ticagrelor plus aspirin were eligible to participate.

Trial inclusion required the presence of at least 1 additional clinical and angiographic feature associated with a high risk of ischemic or bleeding events.
TWILIGHT Inclusion Criteria

**Clinical criteria**

- Age ≥65 years
- Female gender
- Troponin positive ACS
- Established vascular disease (previous MI, documented PAD or CAD/PAD revasc)
- DM treated with medications or insulin
- CKD (eGFR <60ml/min/1.73m² or CrCl <60ml/min)

**Angiographic criteria**

- Multivessel CAD
- Target lesion requiring total stent length >30mm
- Thrombotic target lesion
- Bifurcation lesion(s) with Medina X,1,1 classification requiring ≥2 stents
- Left main (≥50%) or proximal LAD (≥70%) lesions
- Calcified target lesion(s) requiring atherectomy
TWILIGHT - Study Design

**Enrollment Period**
3 Months

High-Risk PCI Patients (N=9006)

Not Randomized (N=1887)

N = 7119

**Randomization Period**
12 Months

Ticagrelor + Aspirin

Ticagrelor + Placebo

**Observation Period**
3 Months

Standard of Care

0 M

3 M

4 M

9 M

15 M

18 M

Standard of Care
## Patient Characteristics

### Baseline Demographics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Tica + Placebo (N = 3555)</th>
<th>Tica + Aspirin (N = 3564)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years [Mean ± SD]</td>
<td>65.2 ± 10.3</td>
<td>65.1 ± 10.4</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>37.1%</td>
<td>36.5%</td>
</tr>
<tr>
<td>Insulin requiring</td>
<td>9.4%</td>
<td>10.5%</td>
</tr>
<tr>
<td>Chronic Kidney Disease</td>
<td>16.8%</td>
<td>16.8%</td>
</tr>
<tr>
<td>Anemia</td>
<td>19.8%</td>
<td>19.1%</td>
</tr>
<tr>
<td>ACS presentation</td>
<td>64.0%</td>
<td>65.7%</td>
</tr>
<tr>
<td>Previous MI</td>
<td>28.7%</td>
<td>28.6%</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>42.3%</td>
<td>42.0%</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>10.2%</td>
<td>9.8%</td>
</tr>
<tr>
<td>Previous major bleed</td>
<td>0.9%</td>
<td>0.9%</td>
</tr>
</tbody>
</table>
Patient Characteristics

### Baseline Procedural Details

<table>
<thead>
<tr>
<th>Variable</th>
<th>Tica + Placebo (N = 3555)</th>
<th>Tica + Aspirin (N = 3564)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radial access</td>
<td>73.1%</td>
<td>72.6%</td>
</tr>
<tr>
<td>Multivessel CAD</td>
<td>63.9%</td>
<td>61.6%</td>
</tr>
<tr>
<td>Lesion morphology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombus</td>
<td>10.4%</td>
<td>10.7%</td>
</tr>
<tr>
<td>Calcification, moderate/severe</td>
<td>14.0%</td>
<td>13.7%</td>
</tr>
<tr>
<td>Any bifurcation</td>
<td>12.2%</td>
<td>12.1%</td>
</tr>
<tr>
<td>Total stent length</td>
<td>40.1 ± 24.2</td>
<td>39.7 ± 24.3</td>
</tr>
<tr>
<td>Calcification, moderate/severe</td>
<td>14.0%</td>
<td>13.7%</td>
</tr>
<tr>
<td>Any bifurcation</td>
<td>12.2%</td>
<td>12.1%</td>
</tr>
<tr>
<td>Chronic total occlusion</td>
<td>6.2%</td>
<td>6.3%</td>
</tr>
<tr>
<td>Total stent length</td>
<td>40.1 ± 24.2</td>
<td>39.7 ± 24.3</td>
</tr>
</tbody>
</table>
Primary Endpoint: BARC 2, 3 or 5 Bleeding

ITT Cohort

Placebo vs Aspirin
HR (95%CI): 0.56 (0.45 to 0.68)
P <0.001

ARD = -3.08% (-4.15% to -2.01%)
NNT = 33
Prespecified Bleeding Endpoints (ITT Cohort)

**BARC 3 or 5**
- Ticagrelor + Placebo: 1.0%
- Ticagrelor + Aspirin: 2.0%
- HR [95%CI]: 0.49 [0.33 - 0.74]
- p = 0.0006

**TIMI major**
- Ticagrelor + Placebo: 0.5%
- Ticagrelor + Aspirin: 1.0%
- HR [95%CI]: 0.50 [0.28 - 0.90]
- p = 0.02

**GUSTO moderate or severe**
- Ticagrelor + Placebo: 0.7%
- Ticagrelor + Aspirin: 1.4%
- HR [95%CI]: 0.53 [0.33 - 0.85]
- p = 0.008

**ISTH major**
- Ticagrelor + Placebo: 1.1%
- Ticagrelor + Aspirin: 2.1%
- HR [95%CI]: 0.54 [0.37 - 0.80]
- p = 0.002
**Key Secondary Endpoint: Death, MI or Stroke**

**PP Cohort**

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>Ticagrelor + Aspirin</th>
<th>Ticagrelor + Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3515</td>
<td>3524</td>
</tr>
<tr>
<td>3</td>
<td>3466</td>
<td>3457</td>
</tr>
<tr>
<td>6</td>
<td>3415</td>
<td>3412</td>
</tr>
<tr>
<td>9</td>
<td>3361</td>
<td>3365</td>
</tr>
<tr>
<td>12</td>
<td>3320</td>
<td>3330</td>
</tr>
</tbody>
</table>

**Cumulative Incidence (%)**

- Placebo vs Aspirin
  - HR (95%CI): 0.99 (0.78 to 1.25)
  - Pnon-inferiority <0.001

**ARD = -0.06% (-0.97% to 0.84%)**
Prespecified Ischemic Endpoints (PP Cohort)

- **CV Death, MI or Ischemic Stroke**
  - Ticagrelor + Placebo: 3.6%
  - Ticagrelor + Aspirin: 3.7%
  - HR [95%CI]: 0.97 [0.76 - 1.24]
  - p = 0.80

- **All-cause Death**
  - Ticagrelor + Placebo: 1.0%
  - Ticagrelor + Aspirin: 1.3%
  - HR [95%CI]: 0.75 [0.48 - 1.18]
  - p = 0.21

- **MI, any**
  - Ticagrelor + Placebo: 2.7%
  - Ticagrelor + Aspirin: 2.7%
  - HR [95%CI]: 1.00 [0.75 - 1.33]
  - p = 0.99

- **Stroke, any**
  - Ticagrelor + Placebo: 0.5%
  - Ticagrelor + Aspirin: 0.3%
  - HR [95%CI]: 0.74 [0.37 - 1.47]
  - p = 0.38

- **Stent thrombosis (definite/probable)**
  - Ticagrelor + Placebo: 0.4%
  - Ticagrelor + Aspirin: 0.6%
  - HR [95%CI]: 1.80 [0.83 - 3.90]
  - p = 0.13
Conclusions

• Importance of aspirin as an antithrombotic agent has been minimized with background therapy with a DOAC or potent P2Y$_{12}$ inhibitor.

• Duration of triple therapy may be very short (2 – 4 weeks) with concomitant DOAC and P2Y$_{12}$.

• Withdrawal of aspirin with continuation of a P2Y$_{12}$ inhibitor alone after a short duration of DAPT lowers bleeding and does not increase ischemic risk, even in high-risk patients, as compared with continuing DAPT.

• The convention of DAPT as the presence of absence of a P2Y$_{12}$ inhibitor may be shifting to presence or absence of aspirin.
THANK YOU!!!