Dual Antiplatelet Therapy in 2019 – The totality of the evidence and its uncertainty

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Medicine Rounds
Sept 24 2019
Conflicts of Interest

I have no known conflicts associated with this presentation and to the best of my knowledge, am equally disliked by

1. All pharmaceutical and device companies
2. Certain professional societies and their guideline writers (likely)
Educational Objectives

Within the context of DAPT for ACS, develop an awareness of:

1. **Clinical uncertainty** that may persist even after apparently large definitive RCTs
2. Importance and various techniques for **evidence synthesis** (fixed & random effects, prediction intervals, network meta-analysis)
3. Potential **limitations** of professional society **guideline** processes
Case presentation

• 72 year old male, non-smoker, presents to ER for new onset exertional dyspnea.

• Negative troponins but symptom reproduced on stress test and electrically positive @ 5 mets

• Sent for cath -> 80% proximal LAD lesion that is stented with 3.5 X 28 mm DES.

• Excellent angiographic result. Sent home the next day on DAPT.

• 5 days later returns to the ER with the same symptoms, except now dyspnea is constant, not worse with activity

• What is your diagnosis & proposed investigations?
Different ADP P2Y12 antagonists
Initial DAPT studies in ACS

- PLATO
  - Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes
  - No. at Risk
    - Ticagrelor: 9333
    - Clopidogrel: 9291
  - Cumulative incidence of primary end point (%)
    - Ticagrelor vs Clopidogrel: p < 0.001

- TRITON-TIMI 38
  - Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes
  - No. at Risk
    - Ticagrelor: 6795
    - Clopidogrel: 6813
  - Primary efficacy end point:
    - Prasugrel vs Clopidogrel: Hazard ratio, 0.81; 95% CI, 0.73-0.90; P = 0.001
  - Key safety end point:
    - Prasugrel vs Clopidogrel: 5.9 vs 4.8; 95% CI, 1.03-1.68; P = 0.03

- Looks impressive both studies p < 0.001 for 1 composite outcome but no effect on mortality for prasugrel
- Elderly under-represented (10-15% > 75)
- Increase in major (life threatening) bleeding
- North American recruitment limited
**TRITON-TIMI 38**

Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes

- CV Death, MI, Stroke (%)
  - Clopidogrel: P=0.03
  - Prasugrel: P=0.01

- TIMI major bleeding
  - P=0.002

- Life threatening

- TIMI major or minor

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**PLATO**

Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes

- CV Death, MI, Stroke (%)
  - Clopidogrel: P=0.33
  - Ticagrelor: P=0.06

- TIMI major bleeding

- Intracranial bleeding

- TIMI major and minor bleeding

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Geographic variation

- (SS) results only in countries where monitoring was done by the sponsor, - results countries monitored by CRO
- 46% of endpoint reduction came from just two countries (Poland and Hungary) who enrolled only 21% of cohort
- FDA “Lack of Robustness of PLATO Superiority with Failure in the US Makes a Confirmatory Study Mandatory.”
- Ignoring heterogeneity leads to an overly precise estimates
Graphical view of meta-analysis

Fixed effects vs Random effects

1. Provides estimate of i) common average effect (fixed effects) or ii) average value of the distribution of effects (random effects)
2. More interesting and clinically relevant is the range of potential values of the next study not its average
Prediction intervals

- The prediction interval in a random-effects model contains highly probable values for the true treatment effects in future settings, if those settings are similar to the settings in the meta-analysis.
- The values in the interval can be compared with clinically relevant thresholds to see whether they correspond to benefit, null effects or harm.
- The prediction interval can be used to estimate the probability that the treatment in a future setting will have a true-positive or true-negative effect, and to perform better power calculations.
PLATO geographic variability – another concern

**PLATO efficacy by geographic regions**

<table>
<thead>
<tr>
<th>Study</th>
<th>Experimental Events</th>
<th>Control Events</th>
<th>Risk Ratio</th>
<th>RR</th>
<th>95%-CI</th>
<th>Weight (fixed)</th>
<th>Weight (random)</th>
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</thead>
<tbody>
<tr>
<td>Plato_asia</td>
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<td>819</td>
<td>0.78</td>
<td>0.78</td>
<td>[0.60; 1.01]</td>
<td>11.1%</td>
<td>15.1%</td>
</tr>
<tr>
<td>Plato_la</td>
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<td>621</td>
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<td>0.87</td>
<td>[0.67; 1.12]</td>
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<td>15.1%</td>
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<td>3820</td>
<td>0.76</td>
<td>0.76</td>
<td>[0.66; 0.88]</td>
<td>36.0%</td>
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<td>0.85</td>
<td>[0.72; 1.00]</td>
<td>27.6%</td>
<td>22.6%</td>
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<tr>
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<td>1.23</td>
<td>[0.91; 1.67]</td>
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<td>12.5%</td>
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<tr>
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<td>60</td>
<td>641</td>
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<td>1.09</td>
<td>[0.77; 1.55]</td>
<td>6.0%</td>
<td>10.3%</td>
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</tbody>
</table>

Fixed effects model: $9333 \times 9291$

Random effects model: $0.85 \times 0.78; 0.92 \times 100.0$

**Prediction interval**

$0.75 \times 1 \times 1.5$

$I^2 = 52.4\%$

**PLATO clinical benefit by geographic regions**

<table>
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<tr>
<th>Study</th>
<th>Experimental Events</th>
<th>Control Events</th>
<th>Risk Ratio</th>
<th>RR</th>
<th>95%-CI</th>
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<th>Weight (random)</th>
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<td>[0.73; 1.04]</td>
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<td>1.00</td>
<td>1.00</td>
<td>[0.85; 1.19]</td>
<td>10.6%</td>
<td>13.6%</td>
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<td>Plato_est</td>
<td>723</td>
<td>3820</td>
<td>0.89</td>
<td>0.89</td>
<td>[0.81; 0.97]</td>
<td>37.8%</td>
<td>28.9%</td>
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<tr>
<td>Plato_west</td>
<td>542</td>
<td>2725</td>
<td>0.93</td>
<td>0.93</td>
<td>[0.84; 1.03]</td>
<td>27.8%</td>
<td>25.0%</td>
</tr>
<tr>
<td>Plato_na</td>
<td>175</td>
<td>707</td>
<td>1.13</td>
<td>1.13</td>
<td>[0.94; 1.37]</td>
<td>8.4%</td>
<td>11.4%</td>
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<tr>
<td>Plato_o</td>
<td>124</td>
<td>641</td>
<td>1.05</td>
<td>1.05</td>
<td>[0.83; 1.32]</td>
<td>5.8%</td>
<td>8.5%</td>
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</tbody>
</table>

Fixed effect model: $9333 \times 9291$

Random effects model: $0.94 \times 0.89; 0.99 \times 100.0$

**Prediction interval**

$0.8 \times 1 \times 1.25$

$I^2 = 33.6\%$
CCS / CJC guidelines 2012 & 2018

PCI for STEMI or NSTEMI

DAPT for 1 year
- ASA 81 mg OD +
- Ticagrelor 90 mg BID or Prasugrel 10 mg OD preferred over
- Clopidogrel 75 mg OD

(Strong Recommendation, High-Quality Evidence)

- Recommend avoid prasugrel with previous TIA or stroke or in non-PCI patients (Strong Recommendation, Moderate-Quality Evidence)

- Clopidogrel only in patients not eligible for ticagrelor or prasugrel (Strong Recommendation, High-Quality Evidence)

- Questionable conclusions - ignores uncertainty due to heterogeneity, lack of generalizability & reproducibility, cost
TC⁴ - A combination of new methods

**Ticagrelor** compared to **clopidogrel** in **acute** coronary syndromes - TC⁴

- Typical RCT difficult to randomize its, many different MDs in acute care settings, expensive follow-up, selected patients
- Typical RCT analysis ignores any pre-existing data
- Solution to recruitment: **cluster randomization**
- Solution to follow-up: **randomized registry**
- Solution to analysis: **Bayesian analysis using prior data**
- Plan: 1.5 year pragmatic cluster randomization (800 patients) for $300K
What’s new from ESC 2019 (based on 35,000 tweets)
ESC 2019 - Birthday party for ticagrelor but few presents

Jay Brophy @brophyj

#ECCongress PLATO 10 year birthday party offering free lunches. But no presents for ticagrelor given losses to prasugrel (nejm.org/doi/full/10.1016/j.heart.2019.02.016) and clopidogrel (tctmd.com/news/popular-a...) in 2 ACS RCTs made public today (1/2)
POPular AGE trial

- Elderly underrepresented
  - TRITON TIMI 38: 13% ≥ 75 years\(^1\)
  - PLATO: 15% ≥ 75 years\(^2\)

- Registry data: ~35% of NSTEMI population is ≥ 75 years

Hypothesis

Clopidogrel is superior in reducing bleeding risk and non-inferior in net clinical benefit compared to ticagrelor/prasugrel in patients of 70 years or older with non-ST-elevation acute coronary syndrome
1278 screened, 1003 randomized

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel (n=501)</th>
<th>Ticagrelor/prasugrel (n=502)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years), median (IQR)</strong></td>
<td>77 (73-81)</td>
<td>77 (73-82)</td>
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<tr>
<td><strong>Male</strong></td>
<td>62.7</td>
<td>64.7</td>
</tr>
<tr>
<td><strong>BMI (kg/m²), mean (SD)</strong></td>
<td>26.5 ± 4.4</td>
<td>26.7 ± 4.8</td>
</tr>
<tr>
<td><strong>Myocardial infarction</strong></td>
<td>24.4</td>
<td>27.1</td>
</tr>
<tr>
<td><strong>PCI</strong></td>
<td>19.6</td>
<td>24.3</td>
</tr>
<tr>
<td><strong>CABG</strong></td>
<td>17.0</td>
<td>17.1</td>
</tr>
<tr>
<td><strong>Ischemic stroke</strong></td>
<td>4.4</td>
<td>5.0</td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td>29.1</td>
<td>29.9</td>
</tr>
<tr>
<td><strong>eGFR &lt;60 (ml/min/1.73m²)</strong></td>
<td>36.1</td>
<td>37.3</td>
</tr>
<tr>
<td><strong>CAG</strong></td>
<td>87.8</td>
<td>90.0</td>
</tr>
<tr>
<td><strong>Radial access</strong></td>
<td>73.7</td>
<td>77.1</td>
</tr>
<tr>
<td><strong>PCI</strong></td>
<td>47.5</td>
<td>48.9</td>
</tr>
<tr>
<td><strong>CABG</strong></td>
<td>15.8</td>
<td>17.4</td>
</tr>
</tbody>
</table>

**PLATO major and minor bleeding**

- Ticagrelor/prasugrel: 23.1%
- Clopidogrel: 17.6%

HR 0.74 (95%CI 0.56-0.97)
P=0.03
• Compared to ticagrelor/prasugrel in the POPular AGE trial we conclude:
  
  – Clopidogrel significantly less bleeding
  – Clopidogrel similar in preventing thrombotic events

• Therefore, we consider clopidogrel the preferred treatment in patients ≥ 70 years with NSTE-ACS
Conclusions: In ACS patients from Japan, Taiwan and South Korea, event rates of primary safety and efficacy endpoints were higher, albeit not significantly, in ticagrelor-treated patients compared with clopidogrel-treated patients. This observation could be explained by the small sample size, imbalance in clinical characteristics and low number of events in the PHILO population. (Circ J 2015; 79: 2452–2460)

Ticagrelor Versus Clopidogrel in Patients With STEMI Treated With Fibrinolysis
TREAT Trial

CONCLUSION Among patients age <75 years with STEMI, administration of ticagrelor after fibrinolytic therapy did not significantly reduce the frequency of cardiovascular events when compared with clopidogrel. (Ticagrelor in Patients With ST Elevation Myocardial Infarction Treated With Pharmacological Thrombolysis [TREAT]; NCT02298088) (J Am Coll Cardiol 2019;73:2819-28) © 2019 by the American College of Cardiology Foundation.
Meta-analysis ACS trials

**Ticagrelor efficacy (RR) in all ACS trials**

<table>
<thead>
<tr>
<th>Study</th>
<th>Experimental Events</th>
<th>Total Events</th>
<th>Control Total</th>
<th>Risk Ratio</th>
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<th>Weight (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLATO_com</td>
<td>864</td>
<td>9333</td>
<td>1014</td>
<td>0.85</td>
<td>0.78</td>
<td>0.92</td>
<td>80.7%</td>
<td>50.4%</td>
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<td>TREAT</td>
<td>129</td>
<td>1913</td>
<td>137</td>
<td>0.93</td>
<td>0.74</td>
<td>1.17</td>
<td>11.1%</td>
<td>25.2%</td>
</tr>
<tr>
<td>PHILO</td>
<td>36</td>
<td>401</td>
<td>25</td>
<td>1.44</td>
<td>0.88</td>
<td>2.35</td>
<td>2.5%</td>
<td>8.3%</td>
</tr>
<tr>
<td>POPULAR</td>
<td>63</td>
<td>502</td>
<td>64</td>
<td>0.98</td>
<td>0.71</td>
<td>1.36</td>
<td>5.7%</td>
<td>16.1%</td>
</tr>
</tbody>
</table>

**Fixed effect model**
- 12149
- 12078

Fixed effects $p < 0.001$
Random effects $p = 0.34$

**Ticagrelor / clopidogrel net clinical benefit (RR) in ACS trial**

<table>
<thead>
<tr>
<th>Study</th>
<th>Experimental Events</th>
<th>Total Events</th>
<th>Control Total</th>
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<th>Weight (random)</th>
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<td>0.88</td>
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<td>160</td>
<td>0.92</td>
<td>0.74</td>
<td>1.14</td>
<td>6.2%</td>
<td>24.9%</td>
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<tr>
<td>PHILO</td>
<td>76</td>
<td>401</td>
<td>51</td>
<td>1.49</td>
<td>1.07</td>
<td>2.06</td>
<td>2.7%</td>
<td>17.2%</td>
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<tr>
<td>POPULAR</td>
<td>103</td>
<td>502</td>
<td>86</td>
<td>1.20</td>
<td>0.92</td>
<td>1.55</td>
<td>4.2%</td>
<td>21.6%</td>
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</table>

**Fixed effect model**
- 12149
- 12078

Fixed effects $p = 0.09$
Random effects $p = 0.51$
Meta-analysis ACS and non-ACS trials

• Results are robust to the inclusion of 14,000 RCT of PVD patients, who have similar baseline event rates

Ticagrelor / clopidogrel efficacy (RR) in ACS and non-ACS Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Experimental Events</th>
<th>Control Events</th>
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<th>RR</th>
<th>95%-CI</th>
<th>Weight (fixed)</th>
<th>Weight (random)</th>
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<tbody>
<tr>
<td>PLATO_com</td>
<td>864</td>
<td>1014</td>
<td>0.85</td>
<td>[0.78; 0.92]</td>
<td>48.9%</td>
<td>33.4%</td>
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<td>TREAT</td>
<td>129</td>
<td>137</td>
<td>0.93</td>
<td>[0.74; 1.17]</td>
<td>6.7%</td>
<td>17.3%</td>
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<tr>
<td>PHILO</td>
<td>36</td>
<td>25</td>
<td>1.44</td>
<td>[0.88; 2.35]</td>
<td>1.5%</td>
<td>5.8%</td>
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<tr>
<td>EUCLID</td>
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<tr>
<td>POPULAR</td>
<td>63</td>
<td>64</td>
<td>0.98</td>
<td>[0.71; 1.36]</td>
<td>3.4%</td>
<td>11.2%</td>
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<tr>
<td>Fixed effect model</td>
<td>19079</td>
<td>19033</td>
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<td>[0.87; 0.99]</td>
<td>100.0%</td>
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<td>Random effects model</td>
<td>--</td>
<td>--</td>
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<td>[0.84; 1.09]</td>
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<td>100.0%</td>
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<tr>
<td>Prediction interval</td>
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<td>--</td>
<td>[0.65; 1.42]</td>
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</table>
CONCLUSIONS

In patients with a myocardial infarction more than 1 year previously, treatment with ticagrelor significantly reduced the risk of cardiovascular death, myocardial infarction, or stroke and increased the risk of major bleeding. (Funded by AstraZeneca; PEGASUS-TIMI 54 Clinical Trial number: NCT01235562)

Composite efficacy 0.85 (0.75–0.96)

- Ticagrelor vs. placebo
- 22 MD authors, everyone has financial COI with the sponsor
METHODS
Ticagrelor in Patients with Stable Coronary Disease and Diabetes
In this randomized, double-blind trial, we assigned patients who were 50 years of age or older and who had stable coronary artery disease and type 2 diabetes mellitus to receive either ticagrelor plus aspirin or placebo plus aspirin. Patients with previous myocardial infarction or stroke were excluded. The primary efficacy outcome was a composite of cardiovascular death, myocardial infarction, or stroke. The primary safety outcome was major bleeding as defined by the Thrombolysis in Myocardial Infarction (TIMI) criteria.
Ticagrelor or Prasugrel in Patients with Acute Coronary Syndromes

**METHODS**

In this multicenter, randomized, open-label trial, we randomly assigned patients who presented with acute coronary syndromes and for whom invasive evaluation was planned to receive either ticagrelor or prasugrel. The primary end point was the composite of death, myocardial infarction, or stroke at 1 year. A major secondary end point (the safety end point) was bleeding.
Totality of the evidence

- 16 (21 if PLATO separated) trials - 203,021 pts, 12 ACS (133,151 pts), 3 CAD, 1 PAD using different comparators

<table>
<thead>
<tr>
<th>Study</th>
<th>year</th>
<th>Ee</th>
<th>Ne</th>
<th>Ec</th>
<th>Nc</th>
<th>Exp</th>
<th>Std</th>
<th>ACS</th>
<th>Be</th>
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<td>Tri_L75</td>
<td>2012</td>
<td>365</td>
<td>3620</td>
<td>397</td>
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<td>C</td>
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<td>C</td>
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<tr>
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<td>121</td>
<td>713</td>
<td>121</td>
<td>730</td>
<td>Pr</td>
<td>C</td>
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<td>EUCLID</td>
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<td>751</td>
<td>6930</td>
<td>740</td>
<td>6955</td>
<td>T</td>
<td>C</td>
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<td>113</td>
<td>109</td>
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<tr>
<td>THEMIS</td>
<td>2019</td>
<td>736</td>
<td>9619</td>
<td>818</td>
<td>9601</td>
<td>T</td>
<td>PI</td>
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<td>100</td>
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<tr>
<td>PEGASUS</td>
<td>2015</td>
<td>980</td>
<td>14095</td>
<td>578</td>
<td>7067</td>
<td>T</td>
<td>PI</td>
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<td>CHARISMA</td>
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<td>534</td>
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<td>C</td>
<td>PI</td>
<td>0</td>
<td>130</td>
<td>104</td>
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</table>
Primary endpoint (all trials) – Network MA

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Comparison: other vs 'Pl' (Random Effects Model)</th>
<th>OR</th>
<th>95%-CI</th>
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<tbody>
<tr>
<td>C</td>
<td></td>
<td>0.847</td>
<td>[0.763; 0.939]</td>
</tr>
<tr>
<td>Pl</td>
<td></td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>Pr</td>
<td></td>
<td>0.742</td>
<td>[0.631; 0.872]</td>
</tr>
<tr>
<td>T</td>
<td></td>
<td>0.818</td>
<td>[0.728; 0.918]</td>
</tr>
</tbody>
</table>

• OR reduction for primary outcome is between 15-25%
• Point estimate shows largest decrease with prasugrel, ticagrelor, clopidogrel order **but**
• Confidence intervals shown overlap and no statistically significant differences
Bleeding endpoint (all trials) – Network MA

- OR increase for major bleeding is between 37-62%
- Moderate heterogeneity between bleeding risks
- Moderate evidence bleeding ticagrelor > clopidogrel
- Inconclusive evidence bleeding prasugrel > clopidogrel
Net clinical benefit (all trials) – Network MA

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Comparison: other vs 'Pl' (Random Effects Model)</th>
<th>OR</th>
<th>95% - CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td></td>
<td>0.894</td>
<td>[0.815; 0.981]</td>
</tr>
<tr>
<td>Pl</td>
<td></td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>Pr</td>
<td></td>
<td>0.817</td>
<td>[0.706; 0.946]</td>
</tr>
<tr>
<td>T</td>
<td></td>
<td>0.926</td>
<td>[0.835; 1.025]</td>
</tr>
</tbody>
</table>

- Strong evidence that clopidogrel and prasugrel have a + net clinical benefit
- Some uncertainty that ticagrelor has + net clinical benefit
- Inconclusive evidence for any net clinical benefit superiority between different DAPT regimes
2018 Canadian Cardiovascular Society Canadian Association of Interventional Cardiology Focused Update of the Guidelines for the Use of Antiplatelet Therapy

Shamir R. Mehta, MD, MSc (co-chair), Stevan R. Barany, MD, Warren J. Cantor, MD, Marie Lordkipanidze, BPharm, MD, Guillaume Marquis-Gravel, MD, Simon D. Robinson, MBChB, MD, Mathes Sibbald, MD, PhD, Derek Y. So, MD, Graham C. Wong, MD, MPH, Joseph G. Abbara, MD, Margaret L. Ackman, PharmD, Alan D. Bell, MD, Raymond Carlier, MD, James D. Douketis, MD, Patrick R. Lawler, MD, MPH, Michael S. McMurray, MD, Jacob A. Udell, MD, Sean van Diepen, MD, Sibbodh Verma, MD, G.B. John Manou, MD, John A. Cairns, MD, and Jean-François Tangasay, MD (co-chair) and members of the Secondary Panel

www.onlinecjc.ca

This reprint is provided with the support of AstraZeneca.
### Ticagrelor / clopidogrel net clinical benefit (RR) in ACS trial (2018)

<table>
<thead>
<tr>
<th>Study</th>
<th>Experimental Events</th>
<th>Control Events</th>
<th>Risk Ratio</th>
<th>RR</th>
<th>95% CI</th>
<th>Weight (fixed)</th>
<th>Weight (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plato asia</td>
<td>177 819</td>
<td>202 812</td>
<td>0.87</td>
<td>0.73</td>
<td>1.04</td>
<td>8.8%</td>
<td>12.3%</td>
</tr>
<tr>
<td>Plato Ta</td>
<td>188 621</td>
<td>186 616</td>
<td>1.00</td>
<td>0.85</td>
<td>1.19</td>
<td>9.6%</td>
<td>12.9%</td>
</tr>
<tr>
<td>Plato est</td>
<td>723 3820</td>
<td>815 3825</td>
<td>0.89</td>
<td>0.81</td>
<td>0.97</td>
<td>34.5%</td>
<td>20.2%</td>
</tr>
<tr>
<td>Plato west</td>
<td>542 2725</td>
<td>578 2704</td>
<td>0.93</td>
<td>0.84</td>
<td>1.03</td>
<td>25.4%</td>
<td>18.7%</td>
</tr>
<tr>
<td>Plato na</td>
<td>175 707</td>
<td>154 706</td>
<td>1.13</td>
<td>0.94</td>
<td>1.37</td>
<td>7.7%</td>
<td>11.4%</td>
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<tr>
<td>Plato o</td>
<td>124 641</td>
<td>116 628</td>
<td>1.05</td>
<td>0.83</td>
<td>1.32</td>
<td>5.3%</td>
<td>9.1%</td>
</tr>
<tr>
<td>TREAT</td>
<td>149 1913</td>
<td>160 1886</td>
<td>0.92</td>
<td>0.74</td>
<td>1.14</td>
<td>6.0%</td>
<td>9.9%</td>
</tr>
<tr>
<td>PHILO</td>
<td>76 401</td>
<td>51 400</td>
<td>1.49</td>
<td>1.07</td>
<td>2.06</td>
<td>2.6%</td>
<td>5.4%</td>
</tr>
</tbody>
</table>

**Fixed effect model**
- 11647 11577
- 0.95 [0.90; 1.00] 100.0%
- --

**Random effects model**
- 0.98 [0.99; 1.07]
- -- 100.0%

**Prediction interval**
- [0.77; 1.24]

---

**PCI for STEMI or NSTEMI**

**DAPT for 1 year**
- ASA 81 mg OD +
- Ticagrelor 90 mg BID or Prasugrel 10 mg OD
- preferred over
- Clopidogrel 75 mg OD
Conflicts of interest – guideline red flags

Box 1: Red flags that should raise substantial skepticism among guideline readers (and medical journals)

✓ Sponsor(s) is a professional society that receives substantial industry funding;
✓ Sponsor is a proprietary company, or is undeclared or hidden
✓ Committee chair(s) have any financial conflict*
✓ Multiple panel members have any financial conflict*
✓ Any suggestion of committee stacking that would pre-ordain a recommendation regarding a controversial topic
✓ No or limited involvement of an expert in methodology in the evaluation of evidence
✓ No external review
✓ No inclusion of non-physician experts/patient representative/community stakeholders
*Includes a panelist with either or both a financial relationship with a proprietary healthcare company and/or whose practice/specialty depends on tests or interventions covered by the guideline

Ensuring the integrity of clinical practice guidelines BMJ 2013

Conflicts of interest

• 2 co-chairs •2 /2
• 20 primary authors •12 / 20
• 9 secondary authors •9 /9
Professional Societies Should Abstain From Authorship of Guidelines and Disease Definition Statements

Guidelines and other statements from professional societies have become increasingly influential. These documents shape how disease should be pre-

John PA Ioannidis
Professor of Medicine, Stanford University (previously at U Ioannina, Greece)
Verified email at stanford.edu

Evidence-based medicine  research methods  meta-analysis  clinical epidemiology  genetic epidemiology

Cited by 182761
Tell us what you really think, John

• Guideline coauthors share in society-wide power game that manipulates disease definition & management

• 10,000’s society members cite them -> a massive, clan-like, group self-citation network

• Guidelines -> promote specialists’ careers, build hierarchies of clan power, boost specialty journals IF but…

• Do they improve medicine or do they homogenize biased, collective, and organized ignorance?

• Professional societies should consider disentangling their specialists from guidelines and disease definitions, & listen to what more impartial stakeholders think

• Professional societies could still fund these efforts without their own experts authoring them
Background

2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

A P2Y12 inhibitor is recommended, in addition to aspirin, for 12 months unless there are contraindications such as excessive risk of bleeds.

Ticagrelor (180 mg loading dose, 90 mg twice daily) is recommended, in the absence of contraindications, for all patients at moderate-to-high risk of ischaemic events (e.g. elevated cardiac troponins), regardless of initial treatment strategy and including those pretreated with clopidogrel (which should be discontinued when ticagrelor is started).

Prasugrel (60 mg loading dose, 10 mg daily dose) is recommended in patients who are proceeding to PCI if no contraindication.

Clopidogrel (300–600 mg loading dose, 75 mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel or who require oral anticoagulation.
Do other guidelines follow the guidelines?

Algorithm for the use of antithrombotic drugs in patients undergoing percutaneous coronary intervention (3)

Antithrombotic Treatment in Patients Undergoing Percutaneous Coronary Intervention

- Treatment Indication
  - NSTE-ACS
  - (Pre-) Treatment DAPT
  - Anticoagulation for PCI
    - UFH
    - Enoxaparin
    - Bivalirudin

- High Bleeding Risk
  - Time
    - No
      - 1 month
        - AT
      - 3 months
        - AT
      - 6 months
        - AT
      - 12 months DAPT
        - AT
      - 6 months DAPT
        - AT
      - 12 months DAPT
        - AT
      - 30 months
        - AT
      - 36 months
        - DAPT >12 months

- Antiplatelet drugs:
  - A: Aspirin
  - C: Clopidogrel
  - P: Prasugrel
  - T: Ticagrelor

www.escardio.org/guidelines

2018 ESC/EACTS Guidelines on myocardial revascularisation
Conclusions 2019

• Synthesis of ACS DAPT trials (>200,000 pts)
  • No evidence of extra benefit with ticagrelor over clopidogrel
  • Possible advantage for prasugrel but selected populations

• Concern about generalizability of RCTs
  • Average age around 64-66, few patients > 75
  • Limited number of women 23-30%
  • < 50% of screened patients recruited, many centers overseas
  • Spin in reporting, COI with sponsors
  • Side effects recording - ISAR (independent) ticagrelor dyspnea withdrawals 2 X rate reported in PLATO (sponsored)

• CCS guideline process & recommendations needs reforming

• Potential bleeding & side effects ^ in unselected older population with more co-morbidities? -> need PE study

• Cost clopidogrel $11, prasugrel $60, ticagrelor $90 -> CAE
Case presentation

- 72 year old male, non-smoker, presents to the ER for new onset exertion dyspnea. Negative troponins. Has exertion dyspnea and electrically positive stress test @ 5 mets
- Sent for cath -> 80% proximal LAD lesion that is stented with 3.5 X 28 mm DES. Excellent angiographic result. Sent home the next day on DAPT.
- 5 days later returns to the ER with the same symptoms.
- What is your diagnosis? **DYSPNEA 2O TICAGRELOR**
- What are your proposed investigations? **EST – 10 METS**
- **TICAGRELOR STOPPED AND WITHIN 72 HOURS ALL SYMPTOMS DISAPPEARED**
“Everybody gets so much information all day long that they lose their common sense” – Gertrude Stein