Advances in Antiplatelet Therapy in PCI and ACS

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Targets for Platelet Inhibition
Limitations of Clopidogrel

1. Delayed onset of action
2. Large interindividual variability in platelet response
3. Irreversibility of inhibitory action
Inhibition of Platelet Aggregation After Loading Dose in Patients With Elective PCI

IPA % (20 µM ADP)

**Prasugrel 60 mg**

**Clopidogrel 600 mg**

***p<0.0001 Prasugrel vs. Clopidogrel

IPA=inhibition of platelet aggregation; PCI=Percutaneous coronary intervention

Healthy Volunteer Crossover Study

From Brandt JT AHJ 153: 66e9, 2007
Ticagrelor and Inhibition of Platelet Aggregation

Gurbel PA al. Circulation 2009
Ticagrelor and Inhibition of Platelet Aggregation in Clopidogrel-Nonresponsive Patients

Gurbel PA et al. *Circulation* 2010;121:1188-99
Clopidogrel vs Prasugrel and Ticagrelor

• **Inhibition of Platelet Aggregation**
  – Prasugrel and ticagrelor show more rapid onset of platelet inhibition than clopidogrel
  – Prasugrel and ticagrelor afford greater inhibition of platelet aggregation than clopidogrel
  – Prasugrel and ticagrelor provide more predictable inhibition of platelet aggregation than clopidogrel

• **Offset of Inhibition of Platelet Aggregation**
  – Ticagrelor shows more rapid offset than clopidogrel after discontinuation
Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes

Stephen D. Wiviott, M.D., Eugene Braunwald, M.D., Carolyn H. McCabe, B.S., Gilles Montalescot, M.D., Ph.D., Witold Ruzyllo, M.D., Shmuel Gottlieb, M.D., Franz-Joseph Neumann, M.D., Diego Ardissino, M.D., Stefano De Servi, M.D., Sabina A. Murphy, M.P.H., Jeffrey Riesmeyer, M.D., Govinda Weerakkody, Ph.D., C. Michael Gibson, M.D., and Elliott M. Antman, M.D., for the TRITON-TIMI 38 Investigators*
Triton TIMI 38 – Prasugrel vs. Clopidogrel

Primary Endpoint: CV Death, MI, Stroke

Primary Endpoint (%)

Days

ITT = 13,608
LTFU = 14 (0.1%)

Prasugrel

Clopidogrel

HR 0.80
P = 0.0003

HR 0.77
P = 0.0001

HR 0.81
(0.73-0.90)
P = 0.0004
NNT = 46

HR 12.1
(781)

9.9
(643)

0
30
60
90
180
270
360
450
<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Risk Reduction (%)</th>
<th>Absolute</th>
<th>Relative</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary: CV death/Nonfatal MI/Nonfatal stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV Death</td>
<td>0.3</td>
<td>11</td>
<td>0.31</td>
<td></td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>2.3</td>
<td>24</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Urgent target vessel revascularization</td>
<td>1.2</td>
<td>34</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>1.3</td>
<td>52</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Recurrent MI followed by CV death</td>
<td>0.3</td>
<td>42</td>
<td>0.02</td>
<td></td>
</tr>
</tbody>
</table>
Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes

Lars Wallentin, M.D., Ph.D., Richard C. Becker, M.D., Andrzej Budaj, M.D., Ph.D., Christopher P. Cannon, M.D., Håkan Emanuelsson, M.D., Ph.D., Claes Held, M.D., Ph.D., Jay Horrow, M.D., Steen Husted, M.D., D.Sc., Stefan James, M.D., Ph.D., Hugo Katus, M.D., Kenneth W. Mahaffey, M.D., Benjamin M. Scirica, M.D., M.P.H., Allan Skene, Ph.D., Philippe Gabriel Steg, M.D., Robert F. Storey, M.D., D.M., and Robert A. Harrington, M.D.
Ticagrelor versus Clopidogrel in ACS

Primary Endpoint: CV Death, MI or Stroke

P<0.001
p=0.0003
HR 0.84 (95% CI 0.77–0.92)
RRR = 16%, ARR = 1.87%, NNT = 54

11.7%
9.8%
Ticagrelor versus Clopidogrel in ACS

**Individual Ischemic Endpoints**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Ticagrelor HR</th>
<th>Clopidogrel HR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Cause Death</td>
<td>0.78 (0.69–0.89)</td>
<td>0.79 (0.69–0.91)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CV Death</td>
<td>0.84 (0.75–0.95)</td>
<td>1.17 (0.91–1.52)</td>
<td>0.22</td>
</tr>
<tr>
<td>MI</td>
<td>0.84 (0.75–0.95)</td>
<td>1.17 (0.91–1.52)</td>
<td>0.22</td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td>1.17 (0.91–1.52)</td>
<td>1.17 (0.91–1.52)</td>
<td>0.74</td>
</tr>
</tbody>
</table>

KM estimated rate (% per year)

- All Cause Death: Ticagrelor 4.5, Clopidogrel 5.9
- CV Death: Ticagrelor 4, Clopidogrel 5.1
- MI: Ticagrelor 5.8, Clopidogrel 6.9
- Stroke: Ticagrelor 1.5, Clopidogrel 1.3
- Ischemic Stroke: Ticagrelor 1.1, Clopidogrel 1.1
Bleeding and in-Hospital Mortality Rates in ACS

24,045 Patients

Major Bleeding: 3.9%
HR=1.64, 95% CI 1.2-2.3

Risk of Bleeding With DAPT

18 RCTs With 129,314 Patients Comparing Single versus Dual Antiplatelet Therapy

![Graph showing risk of bleeding with DAPT compared to single APT.](image)

- **Minor Bleeding**
  - Single APT: 3.4%
  - DAPT: 6.2%
  - RR = 1.56 (1.47-1.66)

- **Major Bleeding**
  - Single APT: 1.4%
  - DAPT: 2.2%
  - RR = 1.47 (1.36-1.60)

- **Fatal Bleeding**
  - Single APT: 0.27%
  - DAPT: 0.3%
  - RR = 1.10 (0.87-1.40)

- **Intracranial Hemorrhage**
  - Single APT: 0.28%
  - DAPT: 0.29%
  - RR = 1.07 (0.85-1.35)

18 RCTs With 129,314 Patients Comparing Single versus Dual Antiplatelet Therapy
Risk of Bleeding With DAPT in Long- versus Short-term Studies


8 RCTs With 91,744 Patients Comparing Single versus Dual Antiplatelet Therapy

### Long-term Studies

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Dual therapy n/N</th>
<th>Monotherapy n/N</th>
<th>OR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CURE</td>
<td>533/6259</td>
<td>317/6303</td>
<td>1.76 [1.52, 2.03]</td>
</tr>
<tr>
<td>CREDO</td>
<td>93/1053</td>
<td>71/1063</td>
<td>1.35 [0.98, 1.87]</td>
</tr>
<tr>
<td>MATCH</td>
<td>73/3793</td>
<td>22/3802</td>
<td>3.37 [2.09, 5.44]</td>
</tr>
<tr>
<td>CHARISMA</td>
<td>164/7802</td>
<td>101/7801</td>
<td>1.64 [1.27, 2.10]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>18907</strong></td>
<td><strong>18969</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 863 (Dual therapy), 511 (Monotherapy)
Test for heterogeneity: Chi² = 9.94, df = 3 (P = 0.02), I² = 69.8%
Test for overall effect: Z = 4.67 (P < 0.00001)

### Short-term Studies

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Dual therapy n/N</th>
<th>Monotherapy n/N</th>
<th>OR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMMII</td>
<td>134/22961</td>
<td>125/22891</td>
<td>1.07 [0.94, 1.37]</td>
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<tr>
<td>CLARITY</td>
<td>33/1752</td>
<td>30/1739</td>
<td>1.09 [0.66, 1.80]</td>
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<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>24713</strong></td>
<td><strong>24630</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 167 (Dual therapy), 155 (Monotherapy)
Test for heterogeneity: Chi² = 0.01, df = 1 (P = 0.94), I² = 0%
Test for overall effect: Z = 0.04 (P = 0.52)

OR = 1.80 (1.40-2.30)

OR = 1.07 (0.86-1.34)
Bleeding Events Safety Cohort

(N=13,457)

TIMI Major Bleeds
Clopidogrel 1.8%
Prasugrel 2.4%
ARD 0.6%
HR 1.32
P=0.03
NNH=167

Life Threatening
Clopidogrel 0.9%
Prasugrel 1.4%
ARD 0.5%
HR 1.52
P=0.01

Nonfatal
Clopidogrel 0.9%
Prasugrel 1.1%
ARD 0.2%
HR 1.52
P=0.23

Fatal
Clopidogrel 0.1%
Prasugrel 0.4%
ARD 0.3%
HR 1.52
P=0.002

ICH
Clopidogrel 0.3%
Prasugrel 0.3%
ARD 0.0%

ICH in Pts w Prior Stroke/TIA (N=518)
Clopidogrel 0.0%
Prasugrel 6.2%
HR 1.5
P=0.02
CABG and Non-CABG Related Bleeding

Triton TIMI 38 – Prasugrel vs. Clopidogrel


HR = 4.73 (1.90–11.82)  
*P* < 0.001

HR = 1.32 (1.03–1.68)  
*P* = 0.03
Early and Late Risks of Prasugrel Over Clopidogrel in ACS Patients Undergoing PCI

Antman E et al. J Am Coll Cardiol 2008;51:2028-33

Major Bleeding

0-3 Days 3-450 Days

HR 1.22 (0.81-1.84) P=0.35
HR 1.39 (1.02-1.89) P=0.036

Prasugrel 0.74
Clopidogrel 0.61
Prasugrel 1.71
Clopidogrel 1.23
Ticagrelor versus Clopidogrel in ACS

CABG and Non-CABG Related Bleeding

Cumulative Incidence of Major Bleeding (%)

<table>
<thead>
<tr>
<th>Months</th>
<th>Ticagrelor</th>
<th>Clopidogrel</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
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<td>3</td>
<td>15</td>
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<td>4</td>
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</tr>
<tr>
<td>12</td>
<td>60</td>
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No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Ticagrelor</th>
<th>Clopidogrel</th>
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<tr>
<td>0</td>
<td>9235</td>
<td>9186</td>
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<td>1</td>
<td>7246</td>
<td>7305</td>
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<tr>
<td>2</td>
<td>6826</td>
<td>6930</td>
</tr>
<tr>
<td>3</td>
<td>6545</td>
<td>6670</td>
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<tr>
<td>4</td>
<td>5129</td>
<td>5209</td>
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<tr>
<td>5</td>
<td>3783</td>
<td>3841</td>
</tr>
<tr>
<td>6</td>
<td>3433</td>
<td>3479</td>
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</tbody>
</table>

p=0.0003
HR 0.84 (95% CI 0.77–0.92)
RRR = 16%, ARR = 1.87%, NNT = 54

11.6% 11.2%
Ticagrelor versus Clopidogrel in ACS

CABG and Non-CABG Related Bleeding

<table>
<thead>
<tr>
<th>Condition</th>
<th>Clopidogrel</th>
<th>Ticagrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plato Major Bleeding</td>
<td>11.2%</td>
<td>11.6%</td>
</tr>
<tr>
<td>Non-CABG PLATO major</td>
<td>3.8%</td>
<td>4.5%</td>
</tr>
<tr>
<td>TIMI Major Bleeding</td>
<td>7.7%</td>
<td>7.9%</td>
</tr>
<tr>
<td>Non-CABG TIMI major</td>
<td>2.2%</td>
<td>2.8%</td>
</tr>
</tbody>
</table>

HR = Hazard Ratio

HR = 1.04 (0.95–1.13) P = 0.43
HR = 1.19 (1.02–1.38) P = 0.03
HR = 1.03 (0.93–1.15) P = 0.57
HR = 1.25 (1.03–1.53) P = 0.03
## Risk of Definite Stent Thrombosis


<table>
<thead>
<tr>
<th></th>
<th>Stable Angina</th>
<th>UA/NSTEMI</th>
<th>STEMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bare Metal Stents</td>
<td>0-0.5%</td>
<td>1.4-1.6%</td>
<td>2.9%</td>
</tr>
<tr>
<td>Drug-Eluting Stents</td>
<td>0.3-0.4%</td>
<td>1.2-1.9%</td>
<td>3.1%</td>
</tr>
</tbody>
</table>

### Risk of Early Stent Thrombosis
Platelet Reactivity and Risk of Early Stent Thrombosis


Multiple Electrode Platelet Aggregometry (Point-of-Care Analysis) -1608 consecutive patients between 02/2007 and 04/2008

\[
\begin{array}{ccc}
\text{Definite ST} & \text{Probable ST} & \text{Definite/ Probable ST} \\
0.2 & 0.2 & 0.4 \\
0.6 & 2.2 & 2.8
\end{array}
\]

\[P<0.0001 \quad P=0.13 \quad P<0.0001\]
Triton TIMI 38 – Prasugrel vs. Clopidogrel

Stent Thrombosis (ARC Definite + Probable)

Any Stent at Index PCI
N= 12,844

Clopidogrel
HR 0.48
P <0.0001
NNT= 77

Prasugrel
1.1 (68)

Days
0 30 60 90 180 270 360 450

Endpoint (%)
0 1 2 3
Ticagrelor versus Clopidogrel in ACS

**Stent Thrombosis**

KM estimated rate (% per year)

- **Definite**
  - Ticagrelor: 1.3
  - Clopidogrel: 1.9
  - HR = 0.67 (0.50–0.91) $P=0.009$

- **Probable or Definite**
  - Ticagrelor: 2.2
  - Clopidogrel: 2.9
  - HR = 0.75 (0.59–0.95) $P=0.02$

- **Definite, Probable or Possible**
  - Ticagrelor: 2.9
  - Clopidogrel: 3.8
  - HR = 0.77 (0.62–0.95) $P=0.01$

Ticagrelor versus Clopidogrel in ACS


**Stent Thrombosis**

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Ticagrelor versus Clopidogrel in ACS


**Stent Thrombosis**

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  - HR = 0.75 (0.59–0.95) $P=0.02$

- **Definite, Probable or Possible**
  - Ticagrelor: 2.9
  - Clopidogrel: 3.8
  - HR = 0.77 (0.62–0.95) $P=0.01$
Adjunctive therapy: primary PCI

- **Aspirin:**
  A bolus of 150-325 mg (chewable) or 250-500 mg i.v. followed by lifelong therapy.  
  - I B

- **Clopidogrel:**
  Bolus (300 mg) or 600 mg.  
  - I C

- **Heparin:**
  100 U/kg (60 U/kg with GP IIb/IIIa)  
  - I C

- **Glycoprotein IIb/IIIa inhibitor**
  Abciximab (60 U/kg with GP IIb/IIIa)  
  - IIa A
TRITON-TIMI 38: Study Design – Distribution of Patients in STEMI Cohort

Double-blind, double-dummy, parallel, randomised controlled trial

All ACS/PCI patients
N = 13608

UA/NSTEMI
n = 10074

Randomised patients with STEMI
N = 3534

Clopidogrel 300 mg LD/75 mg MD
n = 1765

Prasugrel 60 mg LD/10 mg MD
n = 1768

2 patients did not receive study drug or undergo PCI

Primary PCI
n = 2438

Clopidogrel
n = 1235

Prasugrel
n = 1203

Secondary PCI
n = 1094

Clopidogrel
n = 530

Prasugrel
n = 564

Montalescot G et al. Lancet 2009;373(9665):723-731
STEMI Cohort: Primary Endpoint (CV death, MI and Stroke at 15 Months)


- **Primary Endpoint**: CV death, MI and Stroke at 15 Months

**Graph**: Time (days) vs. Proportion of patients (%)

- **Clopidogrel**
  - Proportion at 15 months: 12.4
  - p=0.02
  - RRR=21%

- **Prasugrel**
  - Proportion at 15 months: 10.0
  - p=0.002
  - RRR=32%

**Statistics**

- **HR=0.79 (0.65–0.97)**
- **NNT=42**

**Age-adjusted**

- **HR=0.81 (0.66–0.99)**
- **p=0.002**
- **RRR=32%**
STEMI Cohort: Stent Thrombosis ARC definite/probable


HR = 0.58 (0.36–0.93) NNT = 83

Age-adjusted HR = 0.59 (0.37–0.96)
STEMI Cohort: TIMI Major Non-CABG Bleeding


Proportion of patients (%)

Time (days)

HR = 1.11 (0.70–1.77)  NNH = 333

Age-adjusted HR = 1.19 (0.75–1.89)

Clopidogrel
Prasugrel

p = 0.65

2.4
2.1
Patient disposition

18,758 patients enrolled in PLATO

134 patients not randomized

18,624 patients randomized

NSTEMI/UA/other: 10,194 patients

STEMI: 8,430 patients

Randomized to ticagrelor: efficacy population N= 4,201

Randomized to clopidogrel: efficacy population N= 4,229

No intake of study medication: 36 patients

No intake of study medication: 48 patients

Safety population N=4,165

Safety population N=4,181
Primary endpoint: CV death, MI or stroke

HR: 0.85 (95% CI = 0.74–0.97), p=0.02

No. at risk
Ticagrelor 4,201 3,887 3,834 3,732 3,011 2,297 1,891
Clopidogrel 4,229 3,892 3,823 3,730 3,022 2,333 1,868
All cause mortality

HR 0.82 (95% CI = 0.68–0.99), p=0.04

No. at risk

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<tr>
<th></th>
<th>0</th>
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<th>3</th>
<th>4</th>
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<th>10</th>
<th>11</th>
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<tbody>
<tr>
<td>Ticagrelor</td>
<td>4,201</td>
<td>4,005</td>
<td>3,962</td>
<td>3,876</td>
<td>3,150</td>
<td>2,413</td>
<td>1,993</td>
<td></td>
<td></td>
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<tr>
<td>Clopidogrel</td>
<td>4,229</td>
<td>4,029</td>
<td>3,989</td>
<td>3,912</td>
<td>3,195</td>
<td>2,471</td>
<td>1,980</td>
<td></td>
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</table>
## Stent thrombosis (as per ARC definitions)*

<table>
<thead>
<tr>
<th></th>
<th>Ticagrelor (n=4,201)</th>
<th>Clopidogrel (n=4,229)</th>
<th>HR for ticagrelor (95% CI)</th>
<th>p-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite</td>
<td>1.6</td>
<td>2.5</td>
<td>0.61 (0.42–0.87)</td>
<td>0.01</td>
</tr>
<tr>
<td>Probable or definite</td>
<td>2.5</td>
<td>3.6</td>
<td>0.69 (0.52–0.92)</td>
<td>0.01</td>
</tr>
<tr>
<td>Possible, probable, or definite</td>
<td>3.2</td>
<td>4.4</td>
<td>0.73 (0.56–0.94)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Time-at-risk is calculated from the date of first stent insertion in the study or date of randomization

*Culiti et. al., Circulation. 2007;115:2344–2351

†By univariate Cox model
Primary safety event: major bleeding

HR 0.96 (95% CI = 0.83–1.12), p=0.63

K-M estimated rate (% per year)

No. at risk
Ticagrelor 4,165 3,431 3,254 3,137 2,440 1,786 1,640
Clopidogrel 4,181 3,430 3,297 3,159 2,441 1,804 1,635
Clopidogrel vs Prasugrel

- **Potency**
  - More rapid *onset* of IPA
  - More potent and reliable IPA
  - Irreversible

- **Benefit**
  - Lower rate of MI and ST
  - Similar rate of overall or CV mortality

- **Bleeding**
  - More CABG and non-CABG related major bleeding
  - *caution in patients with unknown coronary anatomy*
  - *caution in patients at high risk of bleeding*

- **STEMI**
  - Benefit without increased bleeding risk

Clopidogrel vs Ticagrelor

- **Potency**
  - More rapid *onset* and *offset* of IPA
  - More potent and reliable IPA
  - Reversible

- **Benefit**
  - Lower rate of MI and ST
  - *Lower overall and CV mortality*

- **Bleeding**
  - *More non-CABG related*
  - *caution in patients at high risk of bleeding*

- **STEMI**
  - Benefit without increased bleeding risk

- **Compliance**
  - *Dyspnea*
  - *Twice daily intake*
# Guideline Recommendations

<table>
<thead>
<tr>
<th>STEMI – Thienopyridine Loading</th>
<th>Clopidogrel 300-600 mg</th>
<th>AHA/ACC</th>
<th>ESC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prasugrel 60 mg</td>
<td>I C</td>
<td>I C/B</td>
<td></td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>I B</td>
<td>IB</td>
<td></td>
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<th>ESC</th>
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<td>IIa C</td>
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<th>UA/NSTEMI – Thienopyridine Loading</th>
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<th>ESC</th>
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<tr>
<td>BMS ≥ 1 month, ideally 12 months</td>
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<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Elective PCI – Thienopyridine Loading</th>
<th>Clopidogrel 300-600 mg</th>
<th>AHA/ACC</th>
<th>ESC</th>
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</tr>
</tbody>
</table>
Incidence of Bleeding in Relation to Antithrombotic Therapy


Yearly incidence (%)

<table>
<thead>
<tr>
<th>Single Therapy</th>
<th>Dual Therapy</th>
<th>Triple Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>2.6</td>
<td>12.3</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>4.6</td>
<td>12</td>
</tr>
<tr>
<td>Vit K Antagonist</td>
<td>4.3</td>
<td></td>
</tr>
<tr>
<td>Aspirin+Clopidogrel</td>
<td>3.7</td>
<td></td>
</tr>
<tr>
<td>Aspirin+Vit K Antagonist</td>
<td>5.1</td>
<td></td>
</tr>
<tr>
<td>Clopidogrel+Vit K Antagonist</td>
<td>12.3</td>
<td></td>
</tr>
<tr>
<td>Aspirin+Clopidogrel+Vit K Antagonist</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>

40 812 patients with MI between 2005-2008
Risk of Bleeding and Mortality After Acute MI in Relation to Antithrombotic Therapy


**A Non-fatal and fatal bleeding**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Hazard ratio (95% CI)</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin alone</td>
<td>1.00</td>
<td>1.00</td>
<td>Reference</td>
</tr>
<tr>
<td>Clopidogrel alone</td>
<td>1.33</td>
<td>1.11</td>
<td>1.59</td>
</tr>
<tr>
<td>Vitamin K antagonist alone</td>
<td>1.23</td>
<td>0.94</td>
<td>1.61</td>
</tr>
<tr>
<td>Aspirin plus clopidogrel</td>
<td>1.47</td>
<td>1.28</td>
<td>1.69</td>
</tr>
<tr>
<td>Aspirin plus vitamin K antagonist</td>
<td>1.84</td>
<td>1.51</td>
<td>2.23</td>
</tr>
<tr>
<td>Clopidogrel plus vitamin K antagonist</td>
<td>3.52</td>
<td>2.42</td>
<td>5.11</td>
</tr>
<tr>
<td>Triple therapy</td>
<td>4.05</td>
<td>3.08</td>
<td>5.33</td>
</tr>
</tbody>
</table>

**B All-cause mortality**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Hazard ratio (95% CI)</th>
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<tr>
<td>Aspirin alone</td>
<td>1.00</td>
<td>1.00</td>
<td>Reference</td>
</tr>
<tr>
<td>Clopidogrel alone</td>
<td>1.01</td>
<td>0.90</td>
<td>1.13</td>
</tr>
<tr>
<td>Vitamin K antagonist alone</td>
<td>0.65</td>
<td>0.56</td>
<td>0.76</td>
</tr>
<tr>
<td>Aspirin plus clopidogrel</td>
<td>0.79</td>
<td>0.72</td>
<td>0.87</td>
</tr>
<tr>
<td>Aspirin plus vitamin K antagonist</td>
<td>0.87</td>
<td>0.77</td>
<td>0.98</td>
</tr>
<tr>
<td>Clopidogrel plus vitamin K antagonist</td>
<td>1.22</td>
<td>0.87</td>
<td>1.70</td>
</tr>
<tr>
<td>Triple therapy</td>
<td>1.04</td>
<td>0.78</td>
<td>1.39</td>
</tr>
</tbody>
</table>
Management of Antithrombotic Therapy in Afib Patients With ACS and/or Undergoing PCI  

<table>
<thead>
<tr>
<th>Hemorrhagic Risk</th>
<th>Clinical Setting</th>
<th>Stent Type</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| Low or intermediate | Elective | BMS | 1 month: ASA, Clop, OAC  
Lifelong: OAC alone |
| | Elective | DES | 3 months: ASA, Clop, OAC  
3-12 months: Clop, OAC  
Lifelong: OAC alone |
| ACS | BMS/DES | 6 months: ASA, Clop, OAC  
6-12 months: Clop, ASA or Clop  
Lifelong: OAC alone |
| High | Elective | BMS | 2-4 weeks: ASA, Clop, OAC  
Lifelong: OAC alone |
| ACS | BMS | 4 weeks: ASA, Clop, OAC  
1-12 months: Clop, ASA or Clop  
Lifelong: OAC alone |
Concurrent DAPT Studies
Timeline to Final Data Collection

DAPT Study, n = 20,165

REAL-LATE, n = 2,000

ZEST-LATE, n = 2,000

OPTIDUAL, n = 1,966

ISAR-SAFE, n = 6,000

ITALIC, n = 3,200

OPTIMIZE, n = 3,120

‘Second Gen.’ DES (Colombo), n = 4,000

ADAPT-DES, n = 11,000

PARIS, n = 5,011

RCT ≥ 12 m

RCT ≤ 12 m

Registries
Triton TIMI 38 – Prasugrel vs. Clopidogrel by Diabetes Status: Primary End Point

Wiviott SD et al. Circulation 2008;118:1626-36

Diabetes Mellitus
HR 0.70 (0.58-0.85), P<0.001

Clopidogrel 17.0

Prasugrel 12.2

No Diabetes Mellitus
HR 0.86 (0.76-0.98), P = 0.02

Clopidogrel 10.6

Prasugrel 9.2

P interaction = 0.09
Triton TIMI 38 – Prasugrel vs. Clopidogrel
Wiviott SD et al. Circulation 2008;118:1626-36

**Non-CABG TIMI Major Bleeding**

Diabetes Mellitus
HR 1.06 (0.66-1.69), P = 0.81

No Diabetes Mellitus
HR 1.43 (1.07-1.91), P = 0.02

\[ P_{interaction} = 0.29 \]
Diabetes as Predictor of Stent Thrombosis

![Graph showing Odds/Hazard Ratio for Diabetes as Predictor of Stent Thrombosis](image)

- OR=2.0 (0.8-4.9)
- OR=2.8 (1.7-4.3)
- OR=2.7 (1.4-5.2)
- HR=3.7 (1.7-7.9)
- HR=2.0 (1.1-3.8)
- HR=2.2 (1.1-4.3)
- HR=1.75 (1.0-3.0)

**References**

- Kuchulakanti, Circ 2006
- Urban, Circ 2006
- Machecourt, JACC 2007
- Iakovou, JAMA 2005
- Daemen, Lancet 2007
- De la Torre, JACC 2008
Triton TIMI 38 – Prasugrel vs. Clopidogrel
Wiviott SD et al. Circulation 2008;118:1626-36

Stent Thrombosis

Diabetes Mellitus
HR 0.52 (0.33-0.84), P = 0.007

No Diabetes Mellitus
HR 0.45 (0.31-0.65), P<0.001

P_interaction = 0.63