Randomised comparison of clopidogrel versus ticagrelor or prasugrel in patients of 70 years or older with non-ST-elevation acute coronary syndrome

POPular AGE trial

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Jurriën ten Berg, Vera Deneer (PIs)
Declaration of interest

- I have nothing to declare
### 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. 

<table>
<thead>
<tr>
<th>I</th>
<th>A</th>
</tr>
</thead>
</table>

- **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).

| I   | B   |

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

| I   | B   |

- **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.

| I   | B   |

Roffi M. 2015 ESC EHJ. 2015.
TRITON-TIMI 38


TIMI major bleeding
Intracranial bleeding
TIMI major and minor bleeding

Clopidogrel
Ticagrelor

P= 0.03
P= 0.06
P= 0.33

PLATO
Bleeding risk

• Major bleeding 5-fold increase in risk of death

• “Nuisance” bleeding → frequent discontinuation P2Y\textsubscript{12} inhibitor → thrombotic risk

Underrepresentation of elderly in RCTs

• Elderly underrepresented
  – TRITON TIMI 38: 13% ≥ 75 years
  – PLATO: 15% ≥ 75 years

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

• Selective inclusion of elderly in RCT’s

1. Wiviott et al. NEJM. 2007;357:2001-15
2. Wallentin et al. NEJM. 2009;361:1045-57
3. De Luca et al. EHJ ACC 2015; 4:441-452
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.
Design

- Randomized
- Open-label
- Independent, blinded clinical event committee
- Funding: ZonMw (projectnumber: 836011016) (Dutch government institution)

**Participating centers**
2. Isala, Zwolle - R.S. Hermanides
3. Meander Medical Center, Amersfoort - E.A. de Vrey
4. Noordwest hospital group, Alkmaar - A.A.C.M. Heestermans
5. Rijnstate, Arnhem - R.M. Tjon Joe Gin
6. Gelre, Apeldoorn - R.A. Waalewijn
7. Medical Center Leeuwarden - S.H. Hofma
9. University Medical Center Leiden - J.W. Jukema
10. Medical Spectrum Twente, Enschede - C. von Birgelen
11. University Medical Center Utrecht - M. Voskuil
Design

Inclusion criteria

- Age ≥ 70 years
- Admitted with NSTE-ACS

Key exclusion criteria

- Contraindication P2Y$_{12}$ inhibitors
- DAPT use prior to admission
- Indication for major surgery
- Life expectancy < 1 year
Design

- ≥ 70 years with NSTE-ACS

  **R 1:1**

  - <72h
  - 12 months

  - Clopidogrel 1dd75
  - Ticagrelor 2dd90 or Prasugrel 1dd5/10

- Choice ticagrelor or prasugrel according to local protocol
Primary endpoint

• PLATO major and minor bleeding

• Net clinical benefit:
  All-cause death, MI, stroke, PLATO major and minor bleeding
Sample size calculation

• Clopidogrel superior in reducing PLATO major and minor bleeding
  ✓ Event rate 10% vs. 17%, 80% power, α 0.05 → n=821

• Clopidogrel non-inferior in net clinical benefit
  ✓ Event rate 30.8% vs. 36.0%, 80% power, α 0.05, non-inferiority threshold 2% → n=1000

1. Wiviott et al. NEJM. 2007;357:2001-15
2. Wallentin et al. NEJM. 2009;361:1045-57
Participants and adherence

≥ 70 years with NSTE-ACS N=1003

R 1:1

Clopidogrel N=501
Adherence 76%

Ticagrelor/Prasugrel N=502
Adherence 51%

June 2013-October 2018

Follow-up 12 months: 99.6% complete
Reasons for switching and discontinuing study medication

- Bleeding
- (N)OAC
- Dyspnea
- No CAD
- CABG
- Side-effects
- Communication error
- Operation
- Recurrent ischemic event
- Other
- Unknown

- Ticagrelor/prasugrel
- Clopidogrel
## Baseline characteristics

<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>
</tr>
<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>
## Baseline characteristics

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<thead>
<tr>
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<th>Clopidogrel (n=501)</th>
<th>Ticagrelor/prasugrel (n=502)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>85.8</td>
<td>85.6</td>
</tr>
<tr>
<td>(N)OAC</td>
<td>16.6</td>
<td>20.3</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td></td>
<td>93.8</td>
</tr>
<tr>
<td>Prasugrel</td>
<td></td>
<td>2.0</td>
</tr>
<tr>
<td>PPI</td>
<td>90.3</td>
<td>90.3</td>
</tr>
<tr>
<td>Diagnosis at discharge</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSTEMI</td>
<td>84.6</td>
<td>83.9</td>
</tr>
<tr>
<td>UA</td>
<td>10.8</td>
<td>10.4</td>
</tr>
<tr>
<td>Other</td>
<td>4.4</td>
<td>5.7</td>
</tr>
</tbody>
</table>
Primary safety outcome

PLATO major and minor bleeding

![Graph showing event rates over follow-up days for Ticagrelor/prasugrel and Clopidogrel.
- Ticagrelor/prasugrel: 23.1% with HR 0.74 (95%CI 0.56-0.97), P=0.03.
- Clopidogrel: 17.6%
]
Secondary safety outcomes

- **PLATO major bleeding**
  - Clopidogrel: 4.4
  - Ticagrelor/prasugrel: 8.0
  - $P=0.02$

- **Intracranial bleeding**
  - Clopidogrel: 0.4
  - Ticagrelor/prasugrel: 1.0
  - $P=0.26$

- **Fatal bleeding**
  - Clopidogrel: 0
  - Ticagrelor/prasugrel: 1.0
  - $P=0.03$

Legend:
- Green: Clopidogrel
- Red: Ticagrelor/prasugrel
Co-primary net clinical benefit outcome

Death, MI, stroke, PLATO major and minor bleeding

ARD -3.4 (95%CI -9.0 – 2.3)
P=0.06*

*P-value for non-inferiority

Ticagrelor/prasugrel

Clopidogrel

Non-inferiority threshold

ESC Congress
Paris 2019
Secondary efficacy outcome

Death, MI, stroke

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Event Rate</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ticagrelor/prasugrel</td>
<td>12.8%</td>
<td>1.02 (0.72-1.45)</td>
<td>0.91</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>12.5%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HR 1.02 (95%CI 0.72-1.45)
P=0.91
Subgroup analysis

PLATO major and minor bleeding

- Diabetes Mellitus: Yes (p = 0.64), No (p = 0.79)
- Prior MI: Yes (p = 0.79), No
- Renal function: eGFR<60 (p = 0.06), eGFR≥60
- Age: ≥80 years (p = 0.85), <80 years
- Gender: Woman (p = 0.79), Man

Net clinical benefit

- Diabetes Mellitus: Yes (p = 0.79), No
- Prior MI: Yes (p = 0.42), No
- Renal function: eGFR<60 (p = 0.21), eGFR≥60
- Age: ≥80 years (p = 0.63), <80 years
- Gender: Woman (p = 0.27), Man

P-value for interaction
Conclusion

• 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
Thank you for your attention

We would like to thank:

- All study patients
- Data Safety Monitoring Board
  - Dr. T. Plokker (chair)
  - Prof. dr. J. G.P. Tijssen
  - Prof. dr. F. Verheugt
- Clinical Event Committee
  - Dr. B.M. Swinkels
  - Dr. E. Bal
  - Dr. C. Zivelonghi
  - Dr. W. Jaarsma
- The POPular AGE study group
### Secondary endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Clopidogrel</th>
<th>Ticagrelor/Prasugrel</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause death</td>
<td>7.4</td>
<td>6.8</td>
<td>1.09 (0.68-1.74)</td>
<td>0.72</td>
</tr>
<tr>
<td>CV death</td>
<td>4.0</td>
<td>3.4</td>
<td>1.18 (0.62-2.25)</td>
<td>0.62</td>
</tr>
<tr>
<td>MI</td>
<td>6.2</td>
<td>6.2</td>
<td>1.01 (0.61-1.66)</td>
<td>0.97</td>
</tr>
<tr>
<td>iCVA</td>
<td>1.0</td>
<td>2.0</td>
<td>0.50 (0.17-1.46)</td>
<td>0.20</td>
</tr>
<tr>
<td>Stenttrombose</td>
<td>1.0</td>
<td>0</td>
<td>65.77 (0.05-87308.30)</td>
<td>0.03</td>
</tr>
<tr>
<td>PLATO minor</td>
<td>11.6</td>
<td>14.9</td>
<td>0.75 (0.53-1.06)</td>
<td>0.10</td>
</tr>
<tr>
<td>PLATO other major</td>
<td>4.8</td>
<td>5.6</td>
<td>0.86 (0.50-1.48)</td>
<td>0.59</td>
</tr>
<tr>
<td>PLATO major life threatening</td>
<td>3.2</td>
<td>5.2</td>
<td>0.62 (0.33-1.15)</td>
<td>0.12</td>
</tr>
<tr>
<td>PLATO non-CABG related major</td>
<td>4.4</td>
<td>8.0</td>
<td>0.55 (0.33-0.92)</td>
<td>0.02</td>
</tr>
<tr>
<td>TIMI non-CABG related major</td>
<td>1.4</td>
<td>3.4</td>
<td>0.41 (0.17-0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td>TIMI major or minor bleeding</td>
<td>5.2</td>
<td>9.2</td>
<td>0.56 (0.35-0.91)</td>
<td>0.02</td>
</tr>
<tr>
<td>ICH</td>
<td>0.4</td>
<td>1.0</td>
<td>0.40 (0.08-2.07)</td>
<td>0.26</td>
</tr>
<tr>
<td>Fatal</td>
<td>0</td>
<td>1.0</td>
<td>0.02 (0-20.41)</td>
<td>0.03</td>
</tr>
</tbody>
</table>
Duration from admittance until receiving the fist dose of study medication:
  – Clopidogrel median 40 (IQR 7-56)
  – Ticagrelor/prasugrel median 3 (IQR 1-29)

Duration from admittance until randomization:
  – Clopidogrel median 26 (IQR 18-49)
  – Ticagrelor/prasugrel median 27 (IQR 18-48)

Mean duration of exposure to study drug was 253±155 days.
97.6% already received a P2Y12 inhibitor before randomization

- Clopidogrel: 71% had to switch after randomization → 30% reloaded
- Ticagrelor/prasugrel: 29% had to switch after randomization → 14% reloaded

Loading dosages of clopidogrel

- 300mg: 41%
- 600mg: 57%
1278 patients ≥ 70 years with NSTE-ACS in St. Antonius hospital

1011 randomized

506 assigned to clopidogrel
- Dropped out: N=5
- Withdrew consent: N=2
- Double randomization: N=1
- Unknown: N=2

501 included in the intention-to-treat analysis

505 assigned to ticagrelor/prasugrel
- Dropped out: N=3
- Withdrew consent: N=1
- Double randomization: N=1
- Unknown: N=1

502 included in the intention-to-treat analysis

Not included
- Contraindication P2Y$_{12}$ inhibitor: N=171
- Declined participation: N=168
- ACS while on DAPT: N=93
- Other: N=54
- Missed: N=51
- Language barrier: N=34
- Dementia/delerium: N=30
- Anemia/thrombocytopenia: N=29
- CRUSADE <31: N=21
- Life-expectancy <1 year: N=15
- Already participated: N=13
- Major surgery planned: N=12
- Active malignancy: N=10
- Reanimation: N=7
- Competing study: N=6
- Shock: N=4

502 included in the intention-to-treat analysis