Practical Application Of New Developments In Antithrombotic And Antiplatelet Therapy In ACS

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Grant/Research Support
Astra Zeneca, Daiichi Sankyo, Eli Lilly, BMS, Terumo, Merck, Medtronic, Boston Scientific

Consulting Fees/Honoraria
11 anti-thrombotic agents with 384 possible treatment combinations

*Ticagrelor is not currently approved for use in any market.

ESC = European Society of Cardiology, LMWH = low-molecular-weight heparin, UFH = unfractionated heparin.
Targets for Antithrombotic Treatment

**Coagulation**
- Warfarin
- Apixaban
- Rivaroxaban
- Edoxaban
- Bivalirudin
- Fondaparinux
- Dabigatran
- LMWH
- Heparin
- AT
- Factor Xa
- Prothrombin
- Thrombin
- Fibrinogen
- Fibrin
- Thrombus

**Platelet activation**
- GP IIb/IIIa inhibitors
- PAR1-inhib
- Clopidogrel
- Prasugrel
- Ticagrelor
- Cangrelor
- Elinogrel
- Vorapaxar
- Atopaxar
- Aspirin
- Tx A₂
- ADP
- Platelet aggregation

**Tissue factor**
- Thrombin
- Plasma clotting cascade

**Conformational activation of GP IIb/IIIa**
- Thrombus
- Fibrin
- Fibrinogen
- Prothrombin

ADP = adenosine diphosphate, AT = antithrombin, GP = glycoprotein, inhib = inhibitor, PAR1 = protease activated receptor, TxA₂ = thromboxane A₂.
Targets for Antithrombotic Treatment

**Coagulation**

- Warfarin
- Rivaroxaban
- Apixaban
- Edoxaban
- Fondaparinux
- LMWH
- Heparin
- Bivalirudin
- Dabigatran

**Platelet activation**

- Tissue factor
- Plasma clotting cascade
- Prothrombin
- Thrombin
- Fibrinogen
- Fibrin
- Thrombus
- Collagen
- Thrombin
- Aspirin
- TxA₂
- PAR1
- ADP
- Conformational activation of GPIIb/IIIa
- Platelet aggregation

**Inhibitors**

- PAR1-inhib
- Vorapaxar
- Atopaxar
- Clopidogrel
- Prasugrel
- Ticagrelor
- Cangrelor
- Elinogrel
- GPIIb/IIIa inhibitors

ADP = adenosine diphosphate, AT = antithrombin, GP = glycoprotein, inhib = inhibitor, PAR1 = protease activated receptor, TxA₂ = thromboxane A₂.
Variability in Inter-Individual Clopidogrel Response

Maximal Aggregation 5 μmol/L ADP (%)

Time from Loading Dose to Catheterization (hr)

n = 1001

ADP, adenosine diphosphate.
# Clopidogrel

## 300 (-600) mg

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<tr>
<th></th>
<th>Standard</th>
<th>Double</th>
<th>HR</th>
<th>95% CI</th>
<th>( P )</th>
<th>Int</th>
<th>( P )</th>
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<td><strong>CV Death / MI / Stroke</strong></td>
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<td>Overall (2N=25,087)</td>
<td>4.4</td>
<td>4.2</td>
<td>0.95</td>
<td>0.84-1.07</td>
<td>0.37</td>
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<td>PCI (2N=17,232)</td>
<td>4.5</td>
<td>3.9</td>
<td>0.86</td>
<td>0.74-0.99</td>
<td>0.04</td>
<td>0.016</td>
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<td>No PCI (2N=7855)</td>
<td>4.2</td>
<td>4.9</td>
<td>1.17</td>
<td>0.95-1.44</td>
<td>0.14</td>
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- **HR**: Hazard Ratio
- **CI**: Confidence Interval
- **P**: Statistical significance

**Cumulative Hazard**

- **CV Death / MI / Stroke**
- **CV Death / MI / Stroke in PCI Patients**

- **Clopidogrel Standard**
  - **HR**: 0.85 (95% CI, 0.74-0.99)
  - **P**: 0.036

- **Clopidogrel Double**
  - **HR**: 0.86 (95% CI, 0.74-0.99)
  - **P**: 0.039

Clopidogrel dosing

Clopidogrel (300-mg loading dose, 75-mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel

A 600-mg loading dose of clopidogrel (or a supplementary 300-mg dose at PCI following an initial 300-mg loading dose) is recommended for patients scheduled for an invasive strategy when ticagrelor or prasugrel is not an option

A higher maintenance dose of clopidogrel 150 mg daily should be considered for the first 7 days in patients managed with PCI and without increased risk of bleeding
PRINCIPLE-TIMI44

(Prasugrel 60 mg)

64.5
74.8
69.3

(Wiviott SD et al. Circulation 2007)

ONSET-OFFSET

Loading Dose

(Ticagrelor (n=54))

(Clopidogrel (n=50))

IPA (20 μM ADP, Final Extent), %

(Gurbel PA et al. Circulation 2009)
TRITON-TIMI 38: study design

ACS (STEMI or UA/NSTEMI) and planned PCI

ASA
N=13,608

Double-blind randomisation

Clopidogrel
300mg loading dose/75mg maintenance
(N=6,795)

Prasugrel
60mg loading dose/10mg maintenance
(N=6,813)

Median duration of therapy: 12 months

1° endpoint: CV death, MI, stroke
2° endpoints: CV death, MI, stroke, recurrent ischaemia with rehospitalisation
            CV death, MI, UTVR
            stent thrombosis (ARC definite/probable)
Safety endpoints: TIMI major bleeds, life-threatening bleeds
Key substudies: pharmacokinetic, genomic

UTVR = urgent target vessel revascularisation

Efficacy endpoints

**CV death, MI, stroke and major non-CABG bleeding**

- **Prasugrel**
  - CV death/MI/stroke: 9.9
  - TIMI major non-CABG bleeds: 2.4

- **Clopidogrel**
  - CV death/MI/stroke: 12.1
  - TIMI major non-CABG bleeds: 1.8

**Early and late stent thrombosis**

- **Early**
  - HR=0.41 (0.29–0.59)
  - p<0.0001

- **Late**
  - HR=0.60 (0.37–0.97)
  - p=0.03

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CABG = coronary artery bypass grafting

Prasugrel

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<tr>
<th>Efficacy endpoints</th>
<th>Clopidogrel</th>
<th>Prasugrel</th>
<th>Hazard ratio (95% CI)</th>
<th>p</th>
<th>Number needed to treat (95% CI)*</th>
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<td>Primary endpoint (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke)</td>
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<td>All STEMI cohort</td>
<td>166 (9.5%)</td>
<td>115 (6.5%)</td>
<td>0.68 (0.54–0.87)</td>
<td>0.0017</td>
<td>35 (24–84)</td>
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<td>Primary PCI</td>
<td>101 (8.2%)</td>
<td>79 (6.6%)</td>
<td>0.80 (0.60–1.08)</td>
<td>0.1440</td>
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<td>Secondary PCI</td>
<td>65 (12.3%)</td>
<td>36 (6.4%)</td>
<td>0.50 (0.34–0.76)</td>
<td>0.0008</td>
<td>17 (12–35)</td>
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<tr>
<th>Timing of study drug administration</th>
<th>Primary (n=2438)</th>
<th>Secondary (n=1094)</th>
<th>p</th>
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<tr>
<td>Before PCI</td>
<td>704 (31%)</td>
<td>204 (19%)</td>
<td>&lt;0.0001</td>
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<tr>
<td>During PCI</td>
<td>1571 (68%)</td>
<td>863 (80%)</td>
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<tr>
<td>After PCI</td>
<td>28 (1%)</td>
<td>8 (1%)</td>
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Conclusions on Prasugrel in ACS

In patients with ACS and planned PCI
Prasugrel 60/10mg vs Clopidogrel 300/75mg for 15 months

- reduces the composite: CV death + MI + stroke
- reduces MI (especially produce related MI)
- reduces stent thrombosis
- raises the risk of major (including fatal) bleeding

with

- higher risk of bleedings at age >75 years, <65 kg, history of stroke or TIA and at CABG
- net clinical benefit larger at STEMI and DM
Prasugrel (60-mg loading dose, 10-mg daily dose) is recommended for P2Y\textsubscript{12}-inhibitor-naïve patients (especially diabetics) in whom coronary anatomy is known and who are proceeding to PCI unless there is a high risk of lifethreatening bleeding or other contraindications.
Primary endpoint:
- Composite of CV death, MI or stroke

Key secondary:
- CV death, MI, or stroke in patients intended for invasive management
- Total mortality, MI or stroke
- CV death, MI, stroke, recurrent ischemia, TIA, or arterial thrombosis
- Components of primary endpoint - CV death; MI; stroke
- Death from any cause

Primary safety:
- Total Major bleeding

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PLATO study design

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

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

Ticagrelor
- 180mg loading dose, then 90mg b.i.d maintenance;
  - (additional 90mg prePCI)

---

Ticagrelor vs. Clopidogrel

Primary Endpoint (CV death, MI, Stroke)

Clopidogrel: 11.7% (HR 0.84, 95% CI: 0.77–0.92, p=0.0003, NNT = 54)
Ticagrelor: 9.8% (HR 1.25, 95% CI: 1.03–1.53, p=0.03, NNH=167)

TIMI Major Non-CABG bleeds

Clopidogrel: 2.3% (HR 0.84, 95% CI: 0.77–0.92, p=0.0003, NNT = 54)
Ticagrelor: 2.8% (HR 1.25, 95% CI: 1.03–1.53, p=0.03, NNH=167)

Ticagrelor vs. Clopidogrel

Primary Endpoint (CV death, MI, Stroke)

CV death

Cumulative incidence (%)

Days after randomization

N=18,624

Definite Stent Thrombosis

Days Since PCI

Definite stent thrombosis, %

Mortality reduction in invasive and non-invasive treatment strategies

Invasive
HR, 0.81, 95% CI: (0.68–0.95)

Number at risk
Invasive
Ticagrelor 6732 6439 6375 6241 5141 3951 3233
Clopidogrel 6676 6376 6331 6209 5114 3917 3164

Non-invasive
HR, 0.75, 95% CI: (0.61–0.93)

N=13408

N=5216

All-cause mortality (%)

0 2 4 6 8 10

Days after randomization
0 60 120 180 240 300 360

Non-invasive
Ticagrelor 2601 2485 2447 2385 1978 1531 1186
Clopidogrel 2615 2488 2448 2380 1965 1524 1200

James S et al. ESC abstract 2010
Prior stroke or TIA

HR, 0.62 (0.42, 0.91)

N=1052

Prior stroke

No prior stroke

James, S et al, ESC 2011
Primary endpoint in ONSET/OFFSET study: Onset: IPA (20 μM ADP, final extent) at 2 h after the first dose of study drug. Offset: Slope of IPA between 4 and 72 h after the last dose of study drug. Ticagrelor (180 mg load, 90 mg bd maintenance dose), clopidogrel (600 mg load, 75 mg/day maintenance dose) or placebo on top of aspirin 75-100 mg/day.

*P<0.001; †P<0.005; ‡P<0.05 ticagrelor vs clopidogrel.

Time from CABG to CV Death (CABG Population)

No. at Risk

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<tr>
<th></th>
<th>Ticagrelor</th>
<th>Clopidogrel</th>
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<tr>
<td>Months from CABG procedure</td>
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<tr>
<td>0</td>
<td>629</td>
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<td>1</td>
<td>583</td>
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<td>2</td>
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<td>4</td>
<td>415</td>
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<td>5</td>
<td>291</td>
<td>269</td>
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<td>6</td>
<td>119</td>
<td>130</td>
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</table>

HR 0.52
(95% CI, 0.32-0.85)

P < 0.01

PLATO dyspnoea

Onset of any dyspnoea AE (%)

Days from first dose

First 30 days

Ticagrelor
Clopidogrel

8.29
3.84

HR(95% CI) = 2.24(1.97–2.54)

p for interaction <0.001

All-cause mortality (%)

Days from randomisation

Ticagrelor mortality

Dyspnoea
No dyspnoea

p for interaction = 0.659
HR(95% CI) = 1.11(0.69–1.78)

HR(95% CI) = 2.73(1.82–4.09)

p for interaction <0.001

All-cause mortality (%)

Days from randomisation

Clopidogrel mortality

Dyspnoea
No dyspnoea

8.51
3.39

AE, adverse event; CI, confidence interval; HR, hazard ratio.
Ticagrelor (180-mg loading dose, 90 mg twice daily) is recommended for all patients at moderate-to-high risk of ischaemic events (e.g. elevated troponins), regardless of initial treatment strategy and including those pretreated with clopidogrel (which should be discontinued when ticagrelor is commenced).
Bivalirudin

30-Day Major Adverse CV Events

Heparin + GPIIb/IIIa inhibitor (n=1802)
Bivalirudin monotherapy (n=1800)

HR=1.00 (95% CI, 0.75, 1.32)
P=0.98

Bivalirudin Should Probably Always Be Combined with UFH

CV = cardiovascular.
Death or Target Lesion Stent Thrombosis

Adjusted N=2996

Bivalirudin, N=1928

Bivalirudin Plus UFH, N=1068

OR; 0.63, 95% CI (0.42-0.94), P=0.025

30 Day Mortality

Number at risk

Bivalirudin 1800 1758 1751 1746 1742 1729 1666
Heparin + GPIIb/IIIa 1802 1764 1748 1736 1728 1707 1630

Death (%) over Time in Days

HR [95%CI] = 0.66 [0.44, 1.00]
P=0.048
A recent study suggested bivalirudin monotherapy as an alternative to UFH plus a GPIIb–IIIa inhibitor.\textsuperscript{255} Significantly lower severe bleeding rates led to a beneficial net clinical outcome indicating that bivalirudin may be preferred in STEMI patients at high risk of bleeding. One-year outcome of the HORIZONS RCT confirmed the beneficial action of bivalirudin monotherapy vs. UFH and a GPIIb–IIIa inhibitor. Uncertainty remains in the early phase of primary PCI, when thrombotic complications seem to be higher with bivalirudin monotherapy. However, this had no effect on long-term clinical outcome, probably because acute in-hospital stent thrombosis can be promptly addressed, unlike late out-of-hospital stent thrombosis.
PRIMARY EFFICACY ENDPOINT:
CV Death / MI / Stroke

Estimated Cumulative Incidence (%)

Placebo

Rivaroxaban (both doses)

Rivaroxaban (2.5 mg)

No. at Risk
Placebo  5113  4307  3470  2664  1831  1079  421
Rivaroxaban  10229  8502  6753  5137  3554  2084  831

Months After Randomization

2 Yr KM Estimate
Placebo  10.7%
Rivaroxaban  8.9%
HR 0.84 (0.74-0.96)

HR and 95% confidence interval estimates from Cox model stratified by thienopyridine use are provided per mITT approach; Stratified log-rank p-values are provided for both mITT and ITT approaches.

HR 0.68  p=0.04

All Cause Death

HR 0.84 (0.74-0.96)
ATLAS-ACS-2
Primary Safety Outcome (Major bleeding)

ICH: 32 (0.6%) with rivaroxaban vs 5 (0.2%) with placebo

SWEDEHEART: Sweden’s new online cardiac registry, the first of its kind

Covering all hospitals in Sweden, SWEDEHEART is unique because it allows long-term follow-up and immediate feedback, says Ulf Stenestrand, MD, PhD, Associate Professor of cardiology and Senior consultant interventional cardiologist, Department of Cardiology, University Hospital, Linköping, Sweden, and President of SWEDEHEART.
Antithrombotic treatment at discharge

**STEMI**

- **Warfarin**
- **Clopidogrel + ASA**
- **ASA**

**NSTEMI**

- **Warfarin**
- **Clopidogrel + ASA**
- **ASA**

Uppsala Clinical Research Centre 2009
ST-elevation or left bundle branch block, <80 years, 1995-2008.

Figure 7a. Acute reperfusion therapy among AMI patients with

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<td>Acute angio without PCI</td>
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Proportion acute reperfusion therapy (%)

0
10
20
30
40
50
60
70
80
90


Uppsala Clinical Research Centre 2009
Mortality in STEMI

Observed
Standardized according to baseline data 2007

1 year

In Hospital

30-days

%
Long-term mortality in STEMI

2.6 years

JAMA. 2011;305(16):1677-1684
Long-term mortality in NSTEMI
Conclusions

• Outcome has improved considerably and mortality has been reduced by almost 50% the last decade

• With the introduction of new more potent anti thrombotic agents with a favourable balance between efficacy and safety mortality can be reduced further