Dual Antiplatelet Therapy in ACS / PCI

Current Recommendations and Corresponding Data

Bernhard Meier
Cardiology
University Hospital Bern
Switzerland
Demand BAYER ASPIRIN

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Pain
Headache
Neuritis
Toothache
Neuralgia
Lumbago
Rheumatism

Aspirin is the trade mark of Bayer Manufacture of Monoaceticacidester of Salicylicacid
AMIS: Impact of Clopidogrel on in-hospital Mortality

ACS
N=26,467

STEMI
N=15,507

With Clopidogrel
N=8060
4.0%

Without Clopidogrel
N=7447
12.4%*

* p<0.001

NSTEMI/UA
N=10,894

With Clopidogrel
N=5338
2.6%

Without Clopidogrel
N=5556
7.8%*

* p<0.001
Mortality and MACE
(death, reinfarction and stroke)
Benefit of Clopidogrel Rx

N=26,467
95% CI
Odds Ratio

†Mortality

†MACE

†Adjusted imbalances for all variables by multivariate analysis
Randomized Study: DES LATE

2701 pts / DES / FU 2 years

12 months vs > 12 months DAT

No benefit of long term DAT
No difference in TIMI Major bleedings

Primary End Point: MI or Death from Cardiac Causes

Cumulative Incidence (%)

Days since Randomization

P = 0.17

Park et al. NEJM 2010
PRODIGY Study

Overall Death, MI or CVA

24 mo DAPT

6 mo DAPT

Hazard Ratio: 0.98 (0.74-1.29)
P=0.91

Valgimigli et al, Circulation 2012
PRODIGY Study

Type II, III or V BARC bleeding

24 mo DAPT

6 mo DAPT

Hazard Ratio: 0.46 (0.1-0.69)
P=0.00018

Valgimigli et al, Circulation 2012
Risk of Bleeding With DAPT

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

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

- **Minor Bleeding**: 3.4% (Single APT), 6.2% (DAPT), RR = 1.85 (1.47-2.34)
  - **Increase**: 56% (RR = 1.56 (1.47-1.66))
- **Major Bleeding**: 1.4% (Single APT), 2.2% (DAPT), RR = 1.57 (1.36-1.80)
  - **Increase**: 55% (RR = 1.55 (1.36-1.77))
- **Fatal Bleeding**: 0.27% (Single APT), 0.3% (DAPT), RR = 1.10 (0.87-1.40)
  - **Increase**: 18% (RR = 1.10 (0.87-1.40))
- **Intracranial Hemorrhage**: 0.28% (Single APT), 0.29% (DAPT), RR = 1.07 (0.85-1.35)
  - **Increase**: 15% (RR = 1.07 (0.85-1.35))

18 RCTs With 129,314 Patients Comparing Single versus Dual Antiplatelet Therapy
Extended dual antiplatelet therapy after PCI with DES
a meta-analysis of randomized trials

Cassese S, Kastrati A, EHJ 2013
Discontinuation of long term clopidogrel therapy induces platelet rebound hyperaggregability between 2 and 6 weeks post cessation. (Diehl P, Clinical Research in Cardiology, April 2011)

Ho PM, JAMA. 2008;299:532-539
Platelet activating substances and targets for inhibition

- Thrombin receptor blockers
  - Direct thrombin inhibitors
    - heparin
    - low molecular weight heparin
    - bivalirudin (po)
    - dabigatran (po)
  - Xa inhibitors
    - rivaroxaban
    - apixaban

- Aspirin (ASA)
- Thromboxane A<sub>2</sub>
- Epinephrine
- Serotonin
- ADP (P<sub>2Y<sub>12</sub>)
- Ticlopidine
- Clopidogrel
- Prasugrel
- Ticagrelor
- Cangrelor (iv)
- Elinogrel (po/iv)
- Thrombin
- PAF
- Collagen

Adapted from Gawaz M, Blood Platelets. 1° Ed. New York: Thieme; 2001
Oral Antiplatelet Agents (via receptor P2Y$_{12}$)

- **Ticagrelor** (Triazolo-Pyrimidine)
- **Prasugrel** (Thienopyridine)
- **Clopidogrel** (Thienopyridine)

**Hydrolysis by esterase**

- CYP-dependent oxidation
  - CYP1A2
  - CYP2B6
  - CYP2C19

**Binding**

- P2Y$_{12}$

**Active compound**

**Intermediate metabolite**

**Prodrug**

**No in vivo biotransformation**

Schömig A

*NEJM 361;11;1108-11*
TRITON-TIMI 38: Landmark Analysis for Primary Efficacy Endpoint

Cardiovascular Death, Nonfatal Myocardial Infarction, Nonfatal Stroke

- Hazard ratios based on Kaplan-Meier estimates; HR = Hazard ratio

Mortality benefit in TRITON

CV-death

- 30 days: Clopidogrel 2.6, Prasugrel 1.6, p=0.044
- 15 months: Clopidogrel 4.3, Prasugrel 3.3, p=0.129
- Diabetes: Clopidogrel 4.2, Prasugrel 3.4, p=0.40

STEMI n = 3534

n = 3146

Montalescot et al, 2009 Lancet 373
Wiviott et al. 2008 Circulation 118
Any cause death, Nonfatal MI, Nonfatal Stroke, Non-CABG TIMI Major Bleed: Post-hoc Analysis Selected Subgroups*

- **History of stroke or TIA**
  - Yes
  - No

- **At least one of Age ≥ 75 y, Body wt. < 60 kg, or History stroke/TIA**
  - Yes
  - No

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Hazard ratio (95% CI)

- **Prasugrel Better**
- **Clopidogrel Better**

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*Kaplan-Meier estimates intention-to-treat cohort

**Tests hazard ratio = 1.0 within subgroups

***Tests equality hazard ratio between subgroups
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

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Prasugrel</th>
<th>Clopidogrel</th>
</tr>
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<tbody>
<tr>
<td>0-3 Days</td>
<td>0.74</td>
<td>0.61</td>
</tr>
<tr>
<td>3-450 Days</td>
<td>1.71</td>
<td>1.23</td>
</tr>
</tbody>
</table>

HR 1.22 (0.81-1.84) P=0.35
HR 1.39 (1.02-1.89) P=0.036
Stent Thrombosis (ARC Definite + Probable)

**Triton-TIMI 38 - Prasugrel vs. Clopidogrel**


Any Stent at Index PCI
N= 12,844

- **Clopidogrel**
  - HR 0.48
  - P <0.0001
  - NNT= 77

- **Prasugrel**
  - 1.1

Days

Endpoint (%)
Coronary Stent Thrombosis

Before DES Introduction
Togni M, Windecker S, Meier B
Curr Interv Cardiol Rep 3: 306-310, 2001

..... in particular, the risk of late stent thrombosis driven by inhibitory effects on endothelial regrowth, or late toxic effects on vascular cells, may be encountered with stent-based drug delivery .....
Development of Oral Anti-Platelet Therapy

- No Tx
- ASA
- Clopidogrel
- Prasugrel
- Ticagrelor
- Vorapaxar

Ischemic Events

Bleeds
Vorapaxar (Thrombin-Receptor (PAR-1) Antagonist) in ACS (TRACER)

- Death (cardiovascular)
- MI
- Stroke

![Graph showing event rates](image)

**Figure 1. Study End Points.**

Shown are Kaplan–Meier event rates at 2 years in the two study groups for the primary efficacy end point (a composite of death from cardiovascular causes, myocardial infarction, stroke, recurrent ischemia with rehospitalization, or urgent coronary revascularization) (Panel A) and the key secondary efficacy end point (a composite of death from cardiovascular causes, myocardial infarction, or stroke) (Panel B).
**Vorapaxar** (Thrombin-Receptor (PAR-1) Antagonist) in ACS (TRACER)

**Figure 2. Risk of Bleeding.**

Shown are Kaplan–Meier event rates at 2 years in the two study groups for Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) criteria for moderate or severe bleeding (Panel A) and for Thrombolysis in Myocardial Infarction (TIMI) criteria for clinically significant bleeding (Panel B).
ACS / AF and New Oral Anticoagulants

ACS trials
- Rivaroxaban: Phase II: ATLAS TIMI 46
- Rivaroxaban: Phase III: ATLAS TIMI 51*
- Apixaban: Phase II: APPRAISE #
- Dabigatran: Phase II: RUBY-1

AF trials
- Rivaroxaban: Phase III: ROCKET-AF
- Apixaban: Phase III: AVERROES##
- Apixaban: Phase III: ARISTOTLE
- Dabigatran: Phase III: RE-LY

* Clinical benefit
# Stopped for bleeding
## Stopped for superiority over ASA

TRILOGY study (< 75 y.o, n=7243)
ACS patients medically managed with prasugrel

No benefit of Prasugrel in ACS patients medically managed

Roe et al, NEJM 2012
## Local Guidelines for Antiplatelet Therapy in ACS patients

### ST-elevation MI

- **Peri-Procedural**
  - ASA 250-500 mg iv
  - Prasugrel 60 mg loading dose irrespective of preloading with clopidogrel

- **Post-Procedural**
  - Prasugrel 10 mg* for ≥1 year
  - ASA indefinitely

### Non ST-elevation MI

- **Peri-Procedural**
  - ASA 250-500 mg iv
  - Clopidogrel 600 mg or prasugrel 60 mg or ticagrelor 180 mg loading dose

- **Post-Procedural**
  - Clopidogrel 75 mg 2x1 for 1 week followed by 75 mg for ≥1 year
  - or
  - Prasugrel 10 mg* for ≥1 year
  - or
  - Ticagrelor 90 mg 2x1 for ≥1 year
  - ASA indefinitely

*5mg in patients with age >75 years or weight <60kg
Contraindication: history of stroke (to be rediscussed)
Trial Design

NON-STEMI / Troponin +, n=4100+ (Clopidogrel naïve or long term 75mg)

Transfer for planned PCI (>2h and <24h)

Randomize

Placebo

Prasugrel 30

CAG

PCI

Prasugrel 60

CAG

PCI

Prasugrel 30

PE: CV-D, MI, Stroke, uTVR, GPI bailout @7d

SE: All TIMI major bleeding @7; NetClinOutcome@30d

30d FU

Stopped prematurely because of pre PCI bleedings

Cathlab

Upstream + Transfer to PCI (>2h to <24h)