Dual vs. Single Antiplatelet Therapy

The GLOBAL LEADERS Study

Stephan Windecker

Department of Cardiology
Swiss Cardiovascular Center and Clinical Trials Unit Bern
Bern University Hospital, Switzerland

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Scientific Advances and Cardiovascular Mortality


- 1954: First open-heart procedure (Gibbon)
- 1958: Coronary arteriography developed (Sones)
- 1961: Risk factors defined
- 1962: First beta-blocker developed (Black)
- 1969: First description of CABG (Favolaro)
- 1972: NHBPEP
- 1976: First HMG CoA reductase inhibitor described (Endo)
- 1980: First implantable cardioverter-defibrillator developed (Mirowski)
- 1985: TIMI 1
- 1986: GISSI and ISIS-2
- 1989: TIMI II
- 1992: SAVE
- 1993: Priority of primary PCI vs. fibrinolysis in acute MI noted
- 2002: ALLHAT
- 2007: Benefit of cardiac resynchronization therapy in heart failure demonstrated
- 2009: Left-ventricular assist device as destination therapy in advanced heart failure shown to be effective
- 2009: Genomewide association in early-onset MI described
- 2009: Deep gene sequencing for responsiveness to cardiovascular drugs performed
Randomised Trial of Intravenous Streptokinase, Oral Aspirin, Both, or Neither among 17187 Cases of Suspected Acute Myocardial Infarction: ISIS-2

ISIS-2 Collaborative Group, Lancet 1988; II:349-360
Aspirin in Secondary Prevention


### 16 secondary prevention trials

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major coronary event</strong> ($\chi^2 = 0.6; p = 0.4$)</td>
<td>880 (4.70)</td>
<td>115 (2.59)</td>
<td>995 (4.30)</td>
</tr>
<tr>
<td><strong>Ischaemic stroke</strong> ($\chi^2 = 0.7; p = 0.4$)</td>
<td>95 (0.51)</td>
<td>45 (1.04)</td>
<td>140 (0.77)</td>
</tr>
<tr>
<td><strong>Serious vascular event</strong> ($\chi^2 = 0.0; p = 1.0$)</td>
<td>226 (6.88)</td>
<td>250 (5.88)</td>
<td>1505 (6.69)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aspirin better</strong></td>
<td>1057 (5.79)</td>
<td>157 (3.36)</td>
<td>1214 (5.30)</td>
</tr>
<tr>
<td><strong>Aspirin worse</strong></td>
<td>0.73 (0.51–1.03)</td>
<td>0.73 (0.50–1.06)</td>
<td>0.78 (0.61–0.99)</td>
</tr>
<tr>
<td><strong>p</strong></td>
<td>0.80 (0.73–0.88)</td>
<td>0.73 (0.50–1.06)</td>
<td>0.81 (0.73–0.90)</td>
</tr>
</tbody>
</table>

**Limited Data on Aspirin After PCI With Stent Implantation!**
Stent-Mediated Arterial Injury

**Arterial Injury**
- Endothelial denudation
- Intima and media laceration

**Thrombosis**
- Platelet adherence and activation
- Thrombus formation
- Growth factors, cytokines

**Inflammation**
- Leucocyte recruitment
- Oxygen radicals
- MMP inhibitors

**Smooth Muscle Cell Proliferation and Migration**

**Cytokines:** PDGF, FGF, TNF-α, IL-6, MCP-1, M-CSF, VEGF
Rationale for DAPT Among Patients Undergoing PCI With Stents

Death, MI, or Revascularization at 30 Days

- ASA+coumarin
- ASA+ticlopidine
- ASA alone

**ISAR**
- ASA+coumarin: 6.2%
- ASA+ticlopidine: 1.6%
- ASA alone: 2.4%

**FANTASTIC**
- ASA+coumarin: 8.6%
- ASA+ticlopidine: 5.7%
- ASA alone: 2.4%

**MATTIS**
- ASA+coumarin: 11%
- ASA+ticlopidine: 5.6%
- ASA alone: 3.6%

**STARS**
- ASA+coumarin: 2.4%
- ASA+ticlopidine: 0.6%
- ASA alone: 3.6%

P-values:
- ISAR: P=0.01
- FANTASTIC: P=0.37
- MATTIS: P=0.07
- STARS: P=0.02, P=0.004

References:
- NEJM 1996
- Circulation 1998
- Circulation 1998
- NEJM 1998
Dual Antiplatelet Therapy

**CURE**
*9-12 months*

RRR=22%

<table>
<thead>
<tr>
<th>Aspirin alone (N=6303)</th>
<th>Aspirin+Clopidogrel (N=6259)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death, MI, stroke</td>
<td>11,4</td>
</tr>
<tr>
<td>MI</td>
<td>9,3</td>
</tr>
<tr>
<td>CV death</td>
<td>6,7</td>
</tr>
<tr>
<td>MI</td>
<td>5,2</td>
</tr>
</tbody>
</table>

**PCI-CURE**
*9-12 months*

RRR=23%

<table>
<thead>
<tr>
<th>Aspirin alone (N=1345)</th>
<th>Aspirin+Clopidogrel (N=1313)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death and MI</td>
<td>8</td>
</tr>
<tr>
<td>MI</td>
<td>6</td>
</tr>
<tr>
<td>CV death</td>
<td>2,3</td>
</tr>
<tr>
<td>MI</td>
<td>2,4</td>
</tr>
</tbody>
</table>

**CREDO**
*9-12 months*

RRR=27%

<table>
<thead>
<tr>
<th>Aspirin alone (N=1063)</th>
<th>Aspirin+Clopidogrel (N=1053)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death, MI, stroke</td>
<td>11,5</td>
</tr>
<tr>
<td>MI</td>
<td>8,5</td>
</tr>
<tr>
<td>CV death</td>
<td>8,4</td>
</tr>
<tr>
<td>MI</td>
<td>6,7</td>
</tr>
</tbody>
</table>

Aspirin alone (N=6303) and Aspirin+Clopidogrel (N=6259) show a reduction in the risk of CV death, MI, and stroke at 9-12 months compared to Aspirin alone (N=1345) and Aspirin+Clopidogrel (N=1313). Similarly, Aspirin alone (N=1063) and Aspirin+Clopidogrel (N=1053) demonstrate a reduction in CV death, MI, and stroke at 9-12 months.
Risk of Bleeding With DAPT

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

↑56%  
RR=1.56  
(1.47-1.66)

↑47%  
RR=1.47  
(1.36-1.60)

RR=1.10  
(0.87-1.40)

RR=1.07  
(0.85-1.35)

Minor Bleeding  
Major Bleeding  
Fatal Bleeding  
Intracranial Hemorrhage

3.4 1.4 0.27 0.28 6.2 2.2 0.3 0.29

0 2 4 6 8

Single APT  
DAPT

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

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Dual therapy</th>
<th>Monotherapy</th>
<th>OR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td></td>
</tr>
<tr>
<td>Long-term Studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CURE</td>
<td>533/6289</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>Subtotal (95% CI)</td>
<td>18907</td>
<td>18969</td>
<td></td>
</tr>
<tr>
<td>Total events:</td>
<td>863 (Dual therapy), 511 (Monotherapy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: Chisq = 9.94, df = 3 (P = 0.02), I^2 = 69.8%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 4.67 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Short-term Studies    |              |             |                   |
|                       | n/N          | n/N         |                   |
| COMMII                | 134/22961    | 125/22891   | 1.07 [0.84, 1.37] |
| CLARITY               | 33/1752      | 30/1739     | 1.09 [0.66, 1.80] |
| Subtotal (95% CI)     | 24713        | 24630       |                   |
| Total events:         | 167 (Dual therapy), 155 (Monotherapy) |
| Test for heterogeneity: Chisq = 0.01, df = 1 (P = 0.94), I^2 = 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)
Dual vs. Single APT: the GLOBAL LEADERS trial

Aspirin

Progress With New DES

Progress With New Antiplatelet Agents
Mode of Action of P2Y$_{12}$ Inhibitors: Clopidogrel, Prasugrel, Ticagrelor


**Limitations of Clopidogrel**

1. Delayed onset of action
2. Large interindividual variability in platelet response
3. Irreversibility of inhibitory action
Ticagrelor and Inhibition of Platelet Aggregation in Clopidogrel-Nonresponsive Patients


IPA (20 μmol/L ADP-Induced Maximum Aggregation) (%)

- **Clopidogrel** → Ticagrelor
- Ticagrelor → **Clopidogrel**

Period 1

- DAY 1
- DAY 14

Crossover

- DAY 15

Period 2

- DAY 28
Ticagrelor and Inhibition of Platelet Aggregation
Gurbel PA al. Circulation 2009
PLATO - Ticagrelor versus Clopidogrel in ACS

Primary Endpoint: CV Death, MI or Stroke

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

No. at Risk
Ticagrelor 9333 8628 8460 8219 6743 5161 4147
Clopidogrel 9291 8521 8362 8124 6650 5096 4047
# Ticagrelor versus Clopidogrel in ACS


## Individual Ischemic Endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Ticagrelor HR (95% CI)</th>
<th>Clopidogrel HR (95% CI)</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>0.75 (0.69–0.89)</td>
<td>0.79 (0.69–0.91)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>MI</td>
<td>0.84 (0.75–0.95)</td>
<td>1.17 (0.91–1.52)</td>
<td>0.74</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.01 (0.83–1.22)</td>
<td>0.84 (0.69–1.03)</td>
<td>0.43</td>
</tr>
</tbody>
</table>

**HR** is Hazard Ratio, **CI** is Confidence Interval.
PLATO – Ticagrelor vs. Clopidogrel

CABG and Non-CABG Related Bleeding

KM estimated rate (% per year)

CABG TIMI Major Bleeding

Non-CABG TIMI Major Bleeding

HR = 0.95
(0.85–1.06)

P = 0.32

HR = 1.25
(1.03–1.53)

P = 0.03
Aspirin dose and ticagrelor benefit in PLATO: fact or fiction?

Source: www.fda.gov/downloads
Clinical Issues With Aspirin

- **Treatment Failure** (“Aspirin Resistance“)
  - Aspirin preparation (ie, enteric coated formulations)
  - Drug-drug interactions (ie, NSAIDs)
  - COX-1 related pathways
  - Medication noncompliance
  - Premature discontinuation

- Irreversible platelet inhibition
- Bleeding risk
- Gastrotoxicity
Risk of Bleeding With Aspirin


**Extracranial Bleeding**

- **PRIMARY PREVENTION**
  - HR (95% CI) = 1.54 (1.30-1.82)
  - P-Heter = 0.20

- **SECONDARY PREVENTION**
  - HR (95% CI) = 2.69 (1.25-5.76)

**Hemorrhagic Stroke**

- **PRIMARY PREVENTION**
  - HR (95% CI) = 1.32 (1.00-1.75)
  - P-Heter = 0.40

- **SECONDARY PREVENTION**
  - HR (95% CI) = 1.67 (0.97-2.90)
Clopidogrel versus Aspirin in Patients with Atherosclerotic Disease – the CAPRIE trial


![Graph showing cumulative risk over time](chart.png)
Clopidogrel versus Aspirin in Patients with Atherosclerotic Disease – the CAPRIE trial


**Relative-risk reduction (%)**

- **Stroke**
- **MI**
- **PAD**
- **All patients**

**Axis:**
- Aspirin better
- Clopidogrel better

**Values:**
- -40 to 40
WOEST trial

573 patients on OAC undergoing stent (DES/BMS) implantation

Follow-up: 1 year

Primary endpoint: any bleeding

Secondary endpoint: ischemic events


* INR as originally indicated

** BMS 1 month
DES and/or ACS 1 year
Primary Endpoint: Total number of bleeding events

Triple therapy group

Double therapy group

p<0.001

HR=0.36  95%CI[0.26-0.50]

NNT = 4

Lancet 2013 in press
Primary Endpoint: Bleeding events TIMI classification

- **Double therapy group**
  - TIMI Minimal: 6.5%
  - TIMI Minor: 11.2%
  - TIMI Major: 3.3%
  - Any TIMI bleeding: 19.5%

- **Triple therapy group**
  - TIMI Minimal: 16.7%
  - TIMI Minor: 27.2%
  - TIMI Major: 5.8%
  - Any TIMI bleeding: 44.9%

Significance levels:
- TIMI Minimal: p<0.001
- TIMI Minor: p=0.001
- TIMI Major: p=0.159
- Any TIMI bleeding: p<0.001
WOEST

Lancet 2013 in press

Secondary Endpoint

MI=any myocardial infarction; TVR= target vessel revascularisation (PCI + CABG); ST= stent thrombosis

Death MI TVR Stroke ST
Double therapy group
Triple therapy group

2.6 6.4 7.3 6.8
p=0.027 p=0.382 p=0.876

4.7
p=0.128

2.9
1.1
p=0.165

3.2
1.5

WOEST  p=0.876
Lancet 2013 in press
Dual vs. Single APT: the GLOBAL LEADERS trial

Aspirin

Progress With New DES

Progress With New Antiplatelet Agents
Arterial Healing After Coronary Stents Implantation

Biolimus Eluted from Biodegradable Polymer versus Sirolimus Eluted from Durable Polymer

Barlis P et al. Eur Heart J 2010

Lesions With At Least 5% Uncovered Struts

-45.5
(-76.9 to –14.3)

P<0.01

Biolimus Stent Sirolimus Stent

29 Lesions 35 Lesions

Biolimus
N=29

Sirolimus
N=35
Biodegradable Polymer Biolimus-Eluting Stents vs Durable Polymer Sirolimus-Eluting Stents

Stefanini G et al. Lancet 2011;378:1940-8

Definite ST - Landmark Analysis @ 1 Year

0 to 1 year RR
0.99 (0.51-1.95)
P=0.98*

1 to 4 year RR
0.20 (0.06-0.67)
P=0.004*

P for interaction=0.017

No. at risk
SES 850 817 801 787 776 759 750 730 714
BES 857 821 804 792 787 780 774 757 746

* P values for superiority
Biodegradable Polymer BES versus Bare Metal Stents in STEMI – COMFORTABLE AMI

Räber L et al. JAMA 2012;308:777-87

1° EP – Cardiac Death, TV-MI or ci-TLR @ 1 Year

1 yr HR
0.49 (0.30-0.80)
P=0.004

MACE (%)

Days since index procedure

No at risk

BMS 582 546 539 531 525 519 514
BES 575 543 541 540 537 534 530

BMS 8.7 %
BES 4.3 %
Definite ST According to Discontinuation of DAPT in the COMFORTABLE-AMI Trial
Räber L et al. JAMA 2012;308:777-87
The purpose of Global LEADERS is to compare:

**Standard 12 months of DAPT following PCI**

(and subsequent maintenance [12 month] antiplatelet therapy with ASA)

with

**A new regimen involving 30 days of DAPT with ASA + ticagrelor**

(and subsequent maintenance [23 month] therapy with ticagrelor)

In an **all-comers** population undergoing PCI with unrestricted biolimus eluting stent (BES) use
Comparative Effectiveness of 2 Pharmaco-Intervention Strategies

All-Comers PCI population
ACS and Elective/Stable patients
*80 centres, 10+ countries, (n=16,000)*

Biolimus-eluting stent (BES)
BioMatrix Flex™

1:1 randomization

**Study Treatment Strategy**
1-month
ASA + Ticagrelor

23-months
monotherapy Ticagrelor

**Reference Treatment Strategy**
12-months DAPT
ACS pts (ASA + Ticagrelor)
Elective pts (ASA + Clopidogrel)

12-months
monotherapy ASA

Primary Endpoint
Study treatment strategy superior to reference treatment strategy on cumulative 2 years composite of all-cause mortality and new Q-wave MI
Study Design Considerations

• **Statistical Considerations**
  – event rate estimated to be 5% at 2 years based on the biolimus eluting stent (BES) arm in the LEADERS Trial, in order to detect a 22.5% relative risk reduction
  – 8000 patients per treatment arm are required to obtain a power >90%

• **Primary Outcome**
  – study treatment strategy superior to reference treatment strategy on cumulative 2 years composite of all cause mortality and new Q-wave MI

• **Key Safety Secondary Endpoint**
  – A composite of BARC 3 or BARC 5 bleeding up to 2 years
Global Leaders Vision

1. Avoid the higher risk of bleeding potentially associated with adding ASA (even low dose) to Ticagrelor

2. Maintain the clinical benefits of potent platelet inhibition after PCI, beyond the initial period of high stent thrombosis risk (30 days)

3. More potent antiplatelet therapy with Ticagrelor may be a better foundation for long term antiplatelet therapy compared to ASA in at-risk patients

4. May pave the way for future studies of Ticagrelor as a single foundation therapy