ADVANCES IN CARDIAC ARRHYTHMIAS
and
GREAT INNOVATIONS IN CARDIOLOGY
XXIX GIORNATE CARDIOLOGICHE TORINESI

Directors
Florenzo Gaita
Sebastiano Marra

Scientific Committee
Malcolm R. Bell, USA
Martin Borggrefe, Germany
Leonardo Calò, Italy
Jean François Leclercq, France
Amir Lerman, USA
Dipen Shah, Switzerland

Organization Committee
Matteo Anselmino, Italy
Carlo Budano, Italy
Davide Castagno, Italy

TURIN
OCTOBER
27-28, 2017
Centro Congressi
Unione Industriale
di Torino

Triple therapy after PCI
Maddalena Lettino, Italy
Disclosure

- **Speaker fee:** Aspen, Astra Zeneca, BMS, Boehringer, Eli Lilly, DaiichiSankio, Bayer, Pfizer, Sanofi
- **Advisory board member:** Astra Zeneca, Eli Lilly, Daiichi Sankyo, BMS, Pfizer, Sanofi
Arterial and venous thrombosis
Epidemiology

Approximately 70-80% of all patients in AF have an indication for continuous OAC

Coronary artery disease co-exists in 34% of patients presenting with AF, with 21% of subjects subsequently requiring PCI or CABG over time

Patients presenting with ACS develop AF in 6-21% of cases

5-7% of pts undergoing PCI have AF or other indications for OAC

With an estimated prevalence of AF in 1-2% of the European population, one to two million anticoagulated patients are candidate for coronary revascularization, often in the form of PCI, usually including stents
“Menage a trois”

- Prevention of stroke $\rightarrow$ anticoagulant
- Prevention of MI/stent thrombosis $\rightarrow$ DAPT
- Prevention of excess bleeding
What is new since 2010?

- **Stents** (newer generation DES are preferable over BMS)
  - New antiplatelet agents
    - New generation P2Y12 inhibitors: prasugrel, ticagrelor, cangrelor
    - Thrombin receptor inhibitors: vorapaxar
  - **NOACs**
    - NOACs for AF
    - NOACs for post-MI secondary prevention
# Key factors for changes

<table>
<thead>
<tr>
<th>Key factors</th>
<th>Suggestion for research</th>
</tr>
</thead>
<tbody>
<tr>
<td>New stents</td>
<td>Stent thrombosis, outcome</td>
</tr>
<tr>
<td>Selection of patients</td>
<td>Risk stratification of pts both for bleeding and for atherothrombotic events</td>
</tr>
<tr>
<td>Antiplatelet therapy</td>
<td>DAPT duration</td>
</tr>
<tr>
<td>Triple therapy</td>
<td>New drugs and new associations</td>
</tr>
<tr>
<td>Can we skip aspirin?</td>
<td>Both in secondary prevention and +OAC/NOAC?</td>
</tr>
</tbody>
</table>
How to reduce the probability of a major bleeding complication?

- Reducing anticoagulation intensity
- Acting on duration of antiplatelet therapy
- Type of stent, PCI or CABG, Vascular access site selection
- Prevention of GI bleeding complications
DAPT after DES: shorter or longer?

LEADERS-FREE and LEADERS FREE II (NCT02843633)
very short duration of DAPT, non inferiority as regards to BMS

GLOBAL LEADERS very short duration of Aspirin treatment
followed by ticagrelor only vs DAPT for one year

NEJM 2015; 373: 2038-47; www.clinicaltrials.gov
DAPT after DES: shorter or longer?

**PEGASUS-TIMI 54 (21162 pts)**

![Graph showing event rates over time for Placebo, Ticagrelor 90 mg, and Ticagrelor 60 mg in the PEGASUS-TIMI 54 study.](image)

- Ticagrelor 90 mg vs. placebo: Hazard ratio 0.83 (95% CI, 0.73–0.96) P=0.008
- Ticagrelor 60 mg vs. placebo: Hazard ratio 0.84 (95% CI, 0.74–0.95) P=0.004

**DAPT (9961 pts)**

**Major Adverse Cardiovascular and Cerebrovascular Events**

- 12–30 mo: Thienopyridine vs. placebo, 4.3% vs. 5.9%; hazard ratio, 0.71; P<0.001
- 12–33 mo: Thienopyridine vs. placebo, 5.6% vs. 6.5%; hazard ratio, 0.82; P=0.02

**Graph showing cumulative incidence rates for Placebo and Thienopyridine in the DAPT study.**

NEJM 2014; 371: 2155-66

NEJM 2015; 372: 1791-800
### Major bleeding

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Triple Therapy</th>
<th>Dual Therapy</th>
<th>Major bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Khuram</td>
<td>2006</td>
<td>5</td>
<td>107</td>
<td>0</td>
</tr>
<tr>
<td>Karjalainen</td>
<td>2007</td>
<td>6</td>
<td>106</td>
<td>3</td>
</tr>
<tr>
<td>DeEugenio</td>
<td>2007</td>
<td>13</td>
<td>86</td>
<td>3</td>
</tr>
<tr>
<td>Saraoff</td>
<td>2008</td>
<td>4</td>
<td>306</td>
<td>3</td>
</tr>
<tr>
<td>Rossini</td>
<td>2008</td>
<td>1</td>
<td>102</td>
<td>1</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td>707</td>
<td>540</td>
<td></td>
</tr>
</tbody>
</table>

**Total events**

- 29 for Triple Therapy
- 10 for Dual Therapy

**Heterogeneity:** Chi² = 7.31, df = 4 (P = 0.12); I² = 45%

**Test for overall effect:** Z = 2.09 (P = 0.04)

**Odds Ratio (M-H Fixed, 95% CI)**
The WOEST trial: results

Lancet 2013; 381: 1107-15
TRIPLE Therapy: OAC + novel antiplatelet agents

Only observational studies; TT vs DT vs DAPT; focus on bleeding complications

TRANSLATE ACS study
11756 pts enrolled in the USA from 2010 to 2012. At discharge: 4.5% received TT with clopidogrel, 0.8% TT with prasugrel, 66% DAPT-clopidogrel and 29% DAPT prasugrel.

JACC Cardiovasc Int 2015; 8: 1880

PRASUGREL
377 pts enrolled from 2009 to 2011
5.6% received a TT with prasugrel.

TIMI major and minor bleeding

JACC 2013; 61: 2060

TICAGRELOL
107 pts on ticagrelor and 159 controls, enrolled in 2013.
TT = warfarin, clopidogrel, ASA
DT = warfarin and ticagrelor

Thromb Res 2015; 135: 26

Major bleeding

<table>
<thead>
<tr>
<th>Days elapsed</th>
<th>Proportion of patients, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td>20</td>
<td>0.00</td>
</tr>
<tr>
<td>40</td>
<td>2.00</td>
</tr>
<tr>
<td>60</td>
<td>4.00</td>
</tr>
<tr>
<td>80</td>
<td>6.00</td>
</tr>
<tr>
<td>100</td>
<td>8.00</td>
</tr>
</tbody>
</table>

TT group

DT group

JACC Cardiovasc Int 2015; 8: 1880
TRIPLE Therapy: NOAC + antiplatelet agents

### RELY trial

<table>
<thead>
<tr>
<th>Aspirin &amp; clopidogrel</th>
<th>Dabigatran 110 mg BID</th>
<th>Dabigatran 150 mg BID</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Annual rate, %</strong></td>
<td>4.72</td>
<td>4.66</td>
<td>5.21</td>
</tr>
<tr>
<td><strong>RR (95% CI) vs warfarin</strong></td>
<td>0.77 (0.50–1.21)</td>
<td>0.81 (0.52–1.26)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No Aspirin &amp; clopidogrel</th>
<th>Dabigatran 110 mg BID</th>
<th>Dabigatran 150 mg BID</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Annual rate, %</strong></td>
<td>2.77</td>
<td>3.24</td>
<td>3.48</td>
</tr>
<tr>
<td><strong>RR (95% CI) vs warfarin</strong></td>
<td>0.81 (0.61–0.94)</td>
<td>0.95 (0.82–1.10)</td>
<td></td>
</tr>
<tr>
<td><strong>P value for interaction</strong></td>
<td>0.8727</td>
<td>0.5167</td>
<td></td>
</tr>
</tbody>
</table>

---

### ARISTOTLE trial

- **Apixaban vs. Warfarin With and Without Aspirin**
- **Adjusted HR** (95% CI) vs warfarin
- **P value for interaction**

---

[Graph showing comparisons between Apixaban vs. Warfarin With and Without Aspirin]
Large-scale outcome studies evaluating combination of NOACs/VKAs and antiplatelets drugs in AF/CAD pts

Completed
PIioneer AF PCI study (NEJM 2016; 375: 2423)
RE-DUAL PCI (NEJM 2017; 377(16): 1513)

Ongoing
AUGUSTUS trial (NCT02415400)

Announced
EVOLVE-AF – PCI
AAA

www.escardio.org/ACCA
## Completed/Ongoing RCTs

<table>
<thead>
<tr>
<th>Study</th>
<th>Anticoagulant</th>
<th>Antiplatelet agent</th>
<th>Duration of DAPT/single drug</th>
<th>Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIONEER-AF PCI</td>
<td>Rivaroxaban</td>
<td>Ticagrelor or prasugrel</td>
<td>1-6-12 months + low dose ASA</td>
<td>WOEST vs ATLAS ACS</td>
</tr>
<tr>
<td>RE-DUAL PCI</td>
<td>Dabigatran</td>
<td>Ticagrelor or prasugrel</td>
<td>1-6-12 months</td>
<td>WOEST</td>
</tr>
<tr>
<td>AUGUSTUS</td>
<td>Apixaban</td>
<td>Ticagrelor or prasugrel</td>
<td>1-6 months</td>
<td>WOEST vs TT</td>
</tr>
</tbody>
</table>
## PIONEER-AF: Improved Safety and Comparable Efficacy vs VKA Plus DAPT

### Endpoints

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>HR</th>
<th>95% CI</th>
<th>HR (95% CI)</th>
<th>Interaction p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinically significant bleeding</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban 15 mg OD plus single antiplatelet vs VKA plus DAPT</td>
<td>0.59</td>
<td>0.47–0.76</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rivaroxaban 2.5 mg BID plus DAPT vs VKA plus DAPT</td>
<td>0.63</td>
<td>0.50–0.80</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Major adverse CV events</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban 15 mg OD plus single antiplatelet vs VKA plus DAPT</td>
<td>1.08</td>
<td>0.69–1.68</td>
<td></td>
<td>0.75</td>
</tr>
<tr>
<td>Rivaroxaban 2.5 mg BID plus DAPT vs VKA plus DAPT</td>
<td>0.93</td>
<td>0.59–1.48</td>
<td></td>
<td>0.77</td>
</tr>
</tbody>
</table>

Both rivaroxaban strategies were associated with a significant reduction in incidence of the primary safety endpoint with comparable incidence of major adverse CV events vs the VKA plus DAPT strategy (trial not powered for efficacy).
RE-DUAL PCI: dabigatran + DAPT

C Secondary Efficacy End Point in Dual-Therapy Groups (Combined) vs. Triple-Therapy Group

Hazard ratio, 1.04 (95% CI, 0.84–1.29)
P=0.005 for noninferiority

Cumulative Incidence of Event (%)

Days to First Event

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Dual therapy (combined)</th>
<th>Triple therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dual therapy</td>
<td>1744</td>
<td>1660</td>
</tr>
<tr>
<td>Triple therapy</td>
<td>981</td>
<td>921</td>
</tr>
</tbody>
</table>

NEJM 2017 DOI: 10.1056/NEJMoa1708454
Objective: Safety of apixaban versus VKA and ASA versus ASA placebo in patients with non-valvular AF undergoing PCI

Population: Patients with non-valvular AF<sup>a</sup> who have undergone PCI with stent placement<sup>b</sup> in previous 2 weeks in whom antiplatelet therapy is planned for 1–6 months<sup>c</sup>

Vascular Pharmacology 2016; 81: 1
Pazienti in terapia con AO e SCA: la survey della European Heart Rhythm Association (EHRA)

A

- Conservative treatment
- PCI on warfarin
- PCI if INR ≤ 3
- PCI with temporary NOAC discontinuation
- Fibrinolytic therapy
- PCI on uninterrupted NOAC

B

- Warfarin
- NOAC

- No additional therapy
- ASA only
- Clopidogrel, prasugrel or ticagrelor only
- ASA + clopidogrel
- ASA + prasugrel
- ASA + heparin
- ASA + clopidogrel + heparin
- ASA + prasugrel (or Ticagrelor) + heparin
- Heparin only
- GPIIb/IIIa inhibitors

STEMI
ESC Focus update on DAPT 2017

Triple Therapy up to 6 mo.
Class Ila B
In Conclusion

• There still are some unmet needs concerning the association of anticoagulation and antiplatelet therapy:
  - a better identification of the bleeding risk of the patient
  - a well defined duration of antiplatelet therapy
  - the optimal dose of novel drugs when they are administered in association

• Both registries and RCTs will probably give us some answers in the future years and will contribute to a better understanding of the pathophysiology of ACS and cardio-embolic disorders
Acute Cardiovascular Care Congress: NOW IN SPRING

“WORKING TOGETHER FOR ACUTE CARDIOVASCULAR PATIENTS”

- >100 international expert faculty
- >60 sessions, workshops and virtual case presentations
- >1100 participants from >80 countries
New-generation DES, ST and mortality

“The current ESC 2017 STEMI guidelines have been updated in light of the results of this registry and other RCTs”