Νεώτερα στα αντιαιμοπεταλιακά - ενδείξεις switching

Periklis A. Davlouros, Assistant Professor of Cardiology
Invasive Cardiology & Congenital Heart Disease
Patras University Hospital
Acute Coronary Syndromes (ACS) Management

- **Coro @ PCI**
  - **STEMI:** pPCI, Thrombolysis & CAG (24 hrs)
  - **NSTEMI/USAP:** 24-72 hrs (based on risk)

- **Coro @ CABG**
  - 16.5% CURE, 6.7% PLATO, 10% NSTEMI/UA very rare in STEMI

- **Coro/non-Coro @ Conservative**
  - **STEMI:** system failure, patient’s delay, comorbidities
  - **NSTEMI/USAP:** system failure, very low or very high (!) risk pts
    - 30-60% of pts in the Western world do not have coro during hospital admission, and 45-60% do not have revasc
Rationale for DAPT following an ACS

- **PCI pts**
  - Prevention of stent thrombosis (ST)
    - Acute, subacute, late, very late
  - Reduce incidence of periprocedural MI

- **CABG, Conservative, and PCI pts**
  - Reduce incidence of recurrent MI
  - Reduce incidence of ischemic Stroke
  - Reduce mortality (?) …
Benefit of clopidogrel in reducing CV death, MI, or stroke in the CURE trial: (A) In pts treated medically (B) In pts undergoing PCI or CABG; (C) In pts undergoing PCI; (D) In pts undergoing CABG

20% relative risk reduction ($P<0.003$)
The primary outcome occurred in 9.3% of pts in the clopidogrel + ASA group and 11.4% in the placebo + ASA group. The primary endpoint—MI/Stroke/CV Death—was significantly reduced with clopidogrel + ASA compared to placebo + ASA (P=0.00009, N=12,562, 20% RRR).

12,562 pts within 24 hours after ACS: clopidogrel (300/75 mg) (6259 pts) or placebo (6303 pts) in addition to aspirin for 3 to 12 months.

*Other standard therapies were used as appropriate.

Benefit of Clopidogrel 600/150 for 7 days in Pts subjected to PCI vs. 300/75, at the expense of an increase in study-defined major bleedings…

- 7855 pts who did not undergo PCI no significant difference in end point…
TRITON-TIMI 38: Effectiveness vs. Safety

For each **death from CV causes** prevented by prasugrel as compared with clopidogrel, approximately one additional episode **of fatal bleeding** was caused by prasugrel.

NNT = 46
NNH = 167

Wiviott SD et al, NEJM 357: 2001-2015
PRASUGREL: Safety concerns...

TRITON-TIMI 38: PRASUGREL
Net Clinical Benefit: Post-hoc Analysis

**Prior Stroke / TIA**
- Yes
- No

**Age**
- ≥ 75
- < 75

**Weight**
- < 60 kg
- ≥ 60 kg

**OVERALL**

P_{int} = .006
Risk, %
- +37
- −16
- −1
- −16
- +3
- −14
- −13

Prasugrel Better

HR
0.5
1
2
Prasugrel Better

Clopidogrel Better
RRR of 18%  RRR of 20%

Loading Dose  Days  Maintenance Dose

Clopidogrel  Prasugrel  Clopidogrel  Prasugrel

HR 0.82  P=0.01  HR 0.80  P=0.003

Wiviott SD et al. NEJM 2007;357:2001-15
The landmark analysis of the rate of MI in the overall TRITON-TIMI 38 study population.

Results driven by reduction in MI...
TRILOGY-ACS: ACS pts @ Conservative Tx Primary Efficacy Endpoint and TIMI Major Bleeding Through 30 Months (Overall population)

HR (95% CI): 0.96 (0.86, 1.07)  
P = 0.45

HR (95% CI): 1.23 (0.84, 1.81)  
P = 0.29
PLATO (planned invasive): Decreased mortality!

14 lives per 1000 treated pts

ALL cause mortality

NNT=71
Non-CABG and CABG-related major bleeding

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<th>Clopidogrel</th>
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<td>4.5</td>
<td>3.8</td>
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p=0.026

NS
Significant CAD, defined as at least one stenosis > 50%, in 94% of those intended for invasive and in 89% of those intended for non-invasive management.
PLATO: Mortality in Patients With CABG (n=1261)

- Ticagrelor (n = 632):
  - Nonvascular deaths: 0.6%
  - Vascular deaths: 4%
  - Total: 4.6%
  - P = 0.009

- Clopidogrel (n = 629):
  - Nonvascular deaths: 1.7%
  - Vascular deaths: 7.5%
  - Total: 9.2%
  - P = 0.075

PLATO: Mortality in Patients With CABG Due to Bleeding or Infection

- Death Caused or Contributed to by Bleeding:
  - Ticagrelor: 1.4%
  - Clopidogrel: 4.6%
  - Statistical significance: P = 0.004

- Death Caused or Contributed to by Infection:
  - Ticagrelor: 1%
  - Clopidogrel: 2.9%
  - Statistical significance: P = 0.00349

Sample size: n = 1261

PLATO: Primary efficacy endpoint over time (composite of CV death, MI or stroke)

0–30 days
RRR of 12%

31–360 days
RRR of 20%

Cumulative incidence (%) vs. Days after randomisation

No. at risk
Ticagrelor 9333
8942 8827 8763
Clopidogrel 9291
8875 8763 8688

No. at risk
8673 8543 8397 7028 6480 4822
8688 8437 8286 6945 6379 4751

(HR=0.88; 95% CI=0.77–1.00; p=0.045)
(HR=0.80; 95% CI=0.70–0.91; p<0.001)
Ticagrelor Benefit Maintained Throughout Year

1st 30 days

Kaplan-Meier Estimated Rate (%)

From Randomization to: | HR | ARR (\%)
---|---|---
Day 30 | 0.88 | 0.6
Day 60 | 0.84 | 1.0
Day 90 | 0.86 | 1.0
Day 120 | 0.86 | 1.1
Day 180 | 0.85 | 1.3
Day 360 | 0.84 | 1.9

No. at risk

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<td>9291</td>
<td>8875</td>
<td>8763</td>
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Ticagrelor (443 / 9333) vs. Clopidogrel (502 / 9291)
Ticagrelor and Prasugrel vs Clopidogrel in Acute Coronary Syndromes

**PLATO**
- **N = 18,624**
- Clopidogrel: 300- to 600-mg LD, 75 mg daily
- Ticagrelor: 180-mg LD, 90 mg twice daily

**HR, 0.84 (95% CI, 0.77-0.92)**
- *P* < .001

**TRITON-TIMI 38**
- **N = 13,608**
- Clopidogrel: 300-mg LD, 75 mg daily
- Prasugrel: 60-mg LD, 10 mg daily

**HR, 0.81 (95% CI, 0.73-0.90)**
- *P* < .001

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“There is no such thing as a free lunch......”

Milton Friedman (Nobel-prize winning economist)
Long-Term DAPT: Bleeding Risk

- **CURE**
  - N = 12,562
  - 1-year follow-up
  - CURE major bleed
  - P = .001
  - 3.7% (ASA + Clopidogrel), 2.7% (ASA + Placebo)

- **CREDO**
  - N = 2116
  - 1-year follow-up TIMI major bleed
  - P = .07
  - 8.8% (ASA + Clopidogrel), 6.7% (ASA + Placebo)

- **CHARISMA**
  - N = 15,603
  - 2.5-year follow-up GUSTO severe + moderate bleed
  - P < .001
  - 3.8% (ASA + Clopidogrel), 2.6% (ASA + Placebo)

References:
TIMI major non-CABG-related bleeding events rate

Acute Coronary Syndromes (ACS)

Switching Scenarios

- **Coro @ PCI**
  - Clopidogrel => NAPA *(Guidelines)*
  - NAPA => Clopidogrel
    - Bleeding
    - Contraindications/special warnings & precautions (Con/SWP)
    - Availability & Costs

- **Coro @ CABG**
  - Prasugrel/Clopidogrel => Ticagrelor *(Guidelines)*
  - NAPA => Clopidogrel

- **Initial conservative approach**
  - Prasugrel/Clopidogrel => Ticagrelor *(Guidelines)*
  - NAPA => Clopidogrel
Acute Coronary Syndromes (ACS)
Switching Scenarios

- NAPA $\Rightarrow$ Clopidogrel (Indications)
  - Safety ?

- Clopidogrel $\Rightarrow$ NAPA (Safety, Costs)
  - Efficacy ?
Switching from Clopidogrel to NAPA: Safety

- Pharmacodynamic studies
  - ACS @ PCI, DM, CRF (HD), HPR pts, Healthy
    - Well tolerated, no major bleeding (TIMI/BARC)
    - Clinical impact on ischemic-bleeding events?

Switching from Clopidogrel to NAPA: Safety

- **PLATO**: 46% of pts randomised to ticagrelor had received clopidogrel at presentation
  - No specific safety concerns reported
- **TRILOGY ACS**: 96% of pts switched to prasugrel 5-10 mg following initial clopidogrel
  - No differential event rate was seen according to clopidogrel pretreatment strata
Increased Platelet Inhibition After Switching From Maintenance Clopidogrel to Prasugrel in Patients With Acute Coronary Syndromes

Results of the SWAP (SWitching Anti Platelet) Study

**Reloading:**
Clopidogrel => Prasugrel

Angiolillo et al, JACC 2010
Pharmacodynamic Effects of Prasugrel Dosing Regimens in Patients on Maintenance Prasugrel Therapy

Results of a Prospective Randomized Study

**Figure 1**

**Study Design**

PCI = percutaneous coronary intervention.
**Figure 3** PRI Values Across Timepoints

**Loading:** Prasugrel => Prasugrel

![Graph showing PRI values across timepoints with comparisons for different doses of prasugrel at baseline, 1 hour, and 4 hours.](image-url)
**Reloading** pts chronically treated with P2Y12 inhibitors and presenting with ACS/PCI: Facing a crossroad?

Different scenarios of reloading a patient presenting on chronic treatment with P2Y12 inhibitors requiring PCI.

PDV = pharmacodynamic value
CLV = clinical value

*Patras University Hospital*

*Dimitrios Alexopoulos, IJC 2013*
STEMI

RELOADED
Switching from NAPA to Clopidogrel

- Bleeding
- Contraindications/special warnings & precautions (Con/SWP)
- Availability & Costs
First and recurrent PLATO major bleeding events were similar with ticagrelor and clopidogrel.

Recurrent bleeding events tended to be infrequent.

- **Ticagrelor**
  - Additional events: 70
  - First events: 961
  - p = 0.89

- **Clopidogrel**
  - Additional events: 68
  - First events: 929
  - p = 0.43

What has changed over time

How much does it cost?

Cost of 28 days treatment (eMIMS, Drug Tariff January 2011)

- ODTicagrelor 90mg BD + aspirin 75mg OD: £54.89
- Prasugrel 10mg OD + aspirin 75mg OD: £47.85
- Clopidogrel 75mg OD (generic): £2.97
- Aspirin 75 mg OD (dispersible): £0.29

N.B. Doses shown are for general comparison only and do not imply therapeutic equivalence. Average daily quantity (ADQ) values are used where available.
Greek AntiPlatelet Registry GRAPE 8
Greek Hospitals @ PCI facilities

- Alexandroupolis
- Athens
- Ioannina
- Iraklion
- Larissa
- Patras
Contraindications and precautions...

Contraindications/Special Warnings and Precautions for Use of Contemporary Oral Antiplatelet Treatment in Patients With Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention – Insights From the GReek AntiPlatelet rEGistry (GRAPE) –

Dimitrios Alexopoulos, MD; Ioanna Xanthopoulou, MD; Spyridon Deftereos, MD; George Sitafidis, MD; Ioannis Kanakakis, MD; Michalis Hamilos, MD; Manolis Vavuranakis, MD; Periklis Davlouros, MD; Ioannis Ntalas, MD; Christos Angelidis, MD; George Hahalis, MD; Filippos Triposkiadis, MD; Panos Vardas, MD; Christodoulos Stefanadis, MD; John A. Goudevenos, MD on behalf of the GRAPE Investigators
Contraindications and SWP…

Figure 2. Prevalence of at least 1 CON/SWP to each P2Y12 inhibitor (as a percentage of the total group) with their overlap, and actual P2Y12 inhibitor prescription rates at discharge (as a percentage of patients in each subgroup). C, clopidogrel; CON, contraindication; P, prasugrel; SWP, special warnings and precautions; T, ticagrelor.
2/3 pts at least 1 CON/SWP for any P2Y12 inhibitor, & 1/3 pts at least 1 CON/SWP to all 3 P2Y12 inhibitors

Prevalence of at least 1 CON/SWP to clopidogrel is lower compared to prasugrel or ticagrelor, with no difference being observed between prasugrel and ticagrelor

Prevalence of Con to clopidogrel-ticagrelor low
Contraindications and precautions...

- Male gender
- Age ≥ 75 years
- Weight < 60 Kg
- Hypertension
- Current smoker
- Prior CABG
- STEMI
- Unstable angina
- Primary PCI
- Previous stroke/TIA
- CrCl < 60 ml/min
- Co-medication ↑ bleeding risk
- History of asthma/COPD
- Geographic region:
  - West Greece
  - Epirus
  - Thessaly/East Macedonia/ Thrace
  - Crete
  - Attica

Adjusted RRs (95% CI) and P-values:

- Male gender: 1.09 (0.43 - 0.67), P = 0.2
- Weight < 60 Kg: 0.78 (0.55 - 1.10), P = 0.2
- Hypertension: 1.007 (0.93 - 1.09), P = 0.9
- Current smoker: 1.02 (0.94 - 1.10), P = 0.7
- Prior CABG: 0.74 (0.49 - 1.13), P = 0.2
- STEMI: 1.08 (0.96 - 1.22), P = 0.2
- Unstable angina: 0.96 (0.84 - 1.10), P = 0.6
- Primary PCI: 1.08 (0.98 - 1.20), P = 0.2
- Previous stroke/TIA: 0.70 (0.49 - 1.01), P = 0.06
- CrCl < 60 ml/min: 0.86 (0.70 - 1.04), P = 0.1
- Co-medication ↑ bleeding risk: 0.22 (0.10 - 0.48), P < 0.001
- History of asthma/COPD: 0.59 (0.43 - 0.80), P = 0.001
- Geographic region:
  - West Greece: 1.45 (1.30 - 1.62), P < 0.001
  - Epirus: 0.57 (0.45 - 0.73), P < 0.001
  - Thessaly/East Macedonia/ Thrace: 1.20 (1.03 - 1.40), P = 0.02
  - Crete: 1.11 (0.92 - 1.33), P = 0.3

Favours clopidogrel use vs. newer P2Y12 inhibitor use.
In PLATO we did not really see the same concerns, so the over-75s were still the same mortality benefit with ticagrelor compared to clopidogrel as seen in the under-75s and so **with ticagrelor, we don't have any particular cautions.**
In the largest trial to date of ACS patients managed medically without revascularization, prasugrel was not statistically different from clopidogrel during 2.5 years of follow-up among patients < 75 years of age.

No statistical differences in major, life-threatening, or fatal bleeding with prasugrel vs. clopidogrel.

Secondary analysis of pts aged >75 years (n=2083), who received 5 mg of prasugrel: In pts > 75 yrs and in pts < 60 kg prasugrel appears to be safe, because there was no increased risk in bleeding.
Implementation of contemporary oral antiplatelet treatment guidelines in patients with acute coronary syndrome undergoing percutaneous coronary intervention: A report from the GReek AntiPlatelet rEgistry (GRAPE)

Dimitrios Alexopoulos a,*, John A. Goudevenos b, Ioanna Xanthopoulou a, Spyridon Defteros c, George Sitafidis d, Ioannis Kanakakis e, Michalis Hamilos f, Haralambos Parissis d, Ioannis V. Ntalias b, Christos Angelidis c, Stylianos Petousis f, Manolis Vavuranakis g, George Hahalis a, Christodoulos Stefanadis g on behalf of the GRAPE Investigators

B

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<td>0.99(0.92-1.07)</td>
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<td>0.68(0.58-0.79)</td>
<td>&lt;0.001</td>
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- Male gender
- Bivalirudin
- STEMI
- Primary PCI
- Condition ↑ bleeding risk
- Co-medication ↑ bleeding risk
- Geographic region*
  - West Greece
  - Epirus
  - Thessaly/East Macedonia/Thrace
  - Crete
  - Attica

Favours inappropriate/less preferable P2Y12 inhibitor selection at discharge
Favours appropriate P2Y12 inhibitor selection at discharge

1

0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0

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Patras University Hospital
Alexopoulos et al.
Contraindications and precautions...

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Favours clopidogrel use
Favours newer P2Y12 inhibitor use
Ticagrelor: Safe in pts with prior stroke?

PLATO: ACS & Stroke/TIA
Cumulative incidence of total mortality in the ticagrelor and clopidogrel groups in patients with a history of prior stroke or TIA and no previous stroke or TIA at baseline

- **RRR 38%**
- **RRR 19%**

- No significant treatment-by-stroke history interaction

Among pts with a prior stroke or TIA, rate of PLATO defined and non-CABG related major bleeding were not significantly different between pts assigned to ticagrelor and clopidogrel.

No of pts with prior stroke in previous ACS trials is low and the number of excess intracranial bleedings by novel dual antiplatelet therapy even much lower.

Routinely treating ACS patients with previous stroke or TIA with novel platelet inhibitors cannot be advised yet…

Verheugt FWA. Beware of novel antiplatelet therapy in ACS patients with previous stroke. Circulation 2012

Patras University Hospital
Contraindications and precautions...

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Patras University Hospital

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<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>1.19 (1.02-1.38)</td>
<td>0.03</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>1.18 (1.05-1.33)</td>
<td>0.005</td>
</tr>
<tr>
<td>STEMI</td>
<td>1.90 (1.43-2.54)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non PCI-capable hospital</td>
<td>0.77 (0.69-0.87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Primary PCI</td>
<td>0.91 (0.69-1.21)</td>
<td>0.5</td>
</tr>
<tr>
<td>STEMI no reperfusion first 24h</td>
<td>0.49 (0.33-0.74)</td>
<td>0.001</td>
</tr>
<tr>
<td>Condition ↑ bleeding risk</td>
<td>1.75 (1.48-2.07)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Co-medications ↑ bleeding risk</td>
<td>1.51 (1.16-1.97)</td>
<td>0.002</td>
</tr>
<tr>
<td>History of asthma/COPD</td>
<td>1.29 (1.05-1.58)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Favours inappropriate/less preferable P2Y12 inhibitor initial selection

Favours appropriate P2Y12 inhibitor initial selection
### Appropriate Selection of Antiplatelets

#### B

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current smoker</td>
<td>0.99 (0.92-1.07)</td>
<td>0.8</td>
</tr>
<tr>
<td>Weight &lt; 60 Kg</td>
<td>0.76 (0.54-1.05)</td>
<td>0.1</td>
</tr>
<tr>
<td>Age ≥ 75 years</td>
<td>0.68 (0.58-0.79)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.13 (1.00-1.27)</td>
<td>0.05</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>1.05 (0.96-1.13)</td>
<td>0.3</td>
</tr>
<tr>
<td>STEMI</td>
<td>1.04 (0.94-1.16)</td>
<td>0.4</td>
</tr>
<tr>
<td>Primary PCI</td>
<td>1.14 (1.02-1.26)</td>
<td>0.02</td>
</tr>
<tr>
<td>Condition ↑ bleeding risk</td>
<td>0.78 (0.64-0.96)</td>
<td>0.02</td>
</tr>
<tr>
<td>Co-medication ↑ bleeding risk</td>
<td>1.45 (1.26-1.66)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Geographic region*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>West Greece</td>
<td>1.30 (1.17-1.44)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Epirus</td>
<td>0.64 (0.52-0.78)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Thessaly/East Macedonia/Thrace</td>
<td>1.20 (1.04-1.38)</td>
<td>0.01</td>
</tr>
<tr>
<td>Crete</td>
<td>1.14 (0.96-1.35)</td>
<td>0.1</td>
</tr>
<tr>
<td>Attica</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

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**Favours inappropriate/less preferable P2Y12 inhibitor selection at discharge**

**Favours appropriate P2Y12 inhibitor selection at discharge**
In-hospital switching of oral P2Y12 inhibitor treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention: Prevalence, predictors and short-term outcome

Dimitrios Alexopoulos, MD, a,i Ioanna Xanthopoulou, MD, a,i Spyridon Deftereos, MD, b,i George Sitafidis, MD, c,i Ioannis Kanakakis, MD, d,i Michalis Hamilos, MD, e,i Christos Angelidis, MD, b,i Stylianos Petousis, MD, e,i Dimitrios Stakos, MD, f,i Haralambos Parissis, MD, c,i Manolis Vavouranakis, MD, g,i Periklis Davlouros, MD, a,i John Goudevenos, MD, h,i and Christodoulos Stefanadis, MD g,i Patras, Athens, Larissa, Iraklion, Alexandroupolis, and Ioannina, Greece

(Am Heart J 2014;167:68-76.e2.)
GRAPE registry: 8 Greek Hospitals @ PCI facilities

Out of 1239 clopidogrel receiving pts, 575 (46.4%) switched to NAPA
Out of 523 pts initially receiving NAPA, 34 (6.5%) switched to clopidogrel

Alexopoulos et al.
Out of 1239 clopidogrel initially receiving pts 575 (46.4%) switched to NAPA

Re-Loading @ NAPA

- 175/320 (54.7%) of pts switched to ticagrelor
- 83/255 (32.5%) of pts switched to prasugrel
- p<0.001
Multivariate analysis of predictive factors of switching to NAPA in pts who were initially treated with clopidogrel…

Out of 1239 clopidogrel initially receiving pts 575 (46.4%) switched to NAPA

<table>
<thead>
<tr>
<th>Factor</th>
<th>Adjusted RRs (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 75 years</td>
<td>0.36(0.28-0.46)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>1.16(1.04-1.30)</td>
<td>0.01</td>
</tr>
<tr>
<td>Non PCI-capable hospital</td>
<td>1.32(1.14-1.53)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Geographic region*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>West Greece</td>
<td>1.44(1.25-1.67)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Epirus</td>
<td>0.42(0.31-0.57)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Thessaly/East Macedonia/Thrace</td>
<td>1.07(0.88-1.29)</td>
<td>0.5</td>
</tr>
<tr>
<td>Crete</td>
<td>1.11(0.84-1.48)</td>
<td>0.5</td>
</tr>
<tr>
<td>Attica</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>
Combined in-hospital and 30-day outcome

Registered
N = 1794

Excluded from analysis in-hospital
In-hospital death without receiving any P2Y12 inhibitor N = 5
Discharged without receiving any P2Y12 inhibitor N = 2

Excluded from analysis at 30-day follow-up
Unavailable follow-up data N = 28
Antiplatelet treatment not kept constant N = 85

Not analyzed
In-hospital P2Y12 switching from a novel agent to clopidogrel N = 31
In-hospital switching between newer P2Y12 inhibitors N = 26

Propensity-matched pairs created among 1617 patients

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In-hospital death without receiving any P2Y12 inhibitor N = 5
Discharged without receiving any P2Y12 inhibitor N = 2

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Unavailable follow-up data N = 28
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Not analyzed
In-hospital P2Y12 switching from a novel agent to clopidogrel N = 31
In-hospital switching between newer P2Y12 inhibitors N = 26

Propensity-matched pairs created among 1617 patients

In-hospital switching from clopidogrel to a novel agent
N = 524

Received only clopidogrel without switching until Day 30
N = 633

Received only prasugrel (N = 140) or ticagrelor (N = 320) without switching until Day 30
N = 460
Combined in-hospital and 30-day outcome

- Available in 1766/1794 (98.4%) pts
- 73 (4.1%) had a MACE
  - 43 in-hospital
  - 30 at 30-day follow-up
- 422 (23.9%) experienced bleeding (any BARC)
  - 116 during index hospitalization
  - 267 at 30-day follow-up
  - 39 both in-hospital and at 30-day follow-up
Combined in-hospital and 30-day outcome

**Table III.** One-month outcome in propensity matched pairs of patients who were only ticagrelor/prasugrel treated or switched from clopidogrel to ticagrelor/prasugrel

<table>
<thead>
<tr>
<th></th>
<th>Prasugrel/ticagrelor treated</th>
<th>Switched from clopidogrel to ticagrelor/prasugrel</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 269</td>
<td>N = 269</td>
<td></td>
</tr>
<tr>
<td><strong>Bleeding BARC</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>type 1</td>
<td>66 (24.5)</td>
<td>62 (23.0)</td>
<td>0.8</td>
</tr>
<tr>
<td>type 2</td>
<td>7 (2.6)</td>
<td>9 (3.3)</td>
<td>0.8</td>
</tr>
<tr>
<td>type 3</td>
<td>4 (1.5)</td>
<td>9 (3.3)</td>
<td>0.3</td>
</tr>
<tr>
<td>any type</td>
<td>77 (28.6)</td>
<td>80 (29.7)</td>
<td>0.9</td>
</tr>
<tr>
<td><strong>MACE</strong></td>
<td>6 (2.2)</td>
<td>4 (1.5)</td>
<td>0.8</td>
</tr>
</tbody>
</table>
Combined in-hospital and 30-day outcome

Table IV. One-month outcome in propensity matched pairs of patients who were only clopidogrel treated or switched from clopidogrel to ticagrelor/prasugrel

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel treated</th>
<th>Switched from clopidogrel to ticagrelor/prasugrel</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 418</td>
<td>N = 418</td>
<td></td>
</tr>
<tr>
<td>Bleeding BARC type 1</td>
<td>37 (8.9)</td>
<td>99 (23.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Bleeding BARC type 2</td>
<td>5 (1.2)</td>
<td>16 (3.8)</td>
<td>.03</td>
</tr>
<tr>
<td>Bleeding BARC type 3</td>
<td>8 (1.9)</td>
<td>13 (3.1)</td>
<td>.4</td>
</tr>
<tr>
<td>Bleeding BARC any type</td>
<td>50 (12.0)</td>
<td>128 (30.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>MACE</td>
<td>16 (3.8)</td>
<td>5 (1.2)</td>
<td>.03</td>
</tr>
</tbody>
</table>
Conclusions

- Switching Clopidogrel to NAPA (Efficacy)
  - Mostly within guidelines
  - Safe

- Switching NAPA to Clopidogrel (Safety/Costs)
  - Bleeding (Appropriate?)
  - Con/SWP (Appropriate?)
  - Availability, Costs (Hybrid scenarios?)
PATRINO KARNAVALI 2014
17.01
02.03
Use of Ticagrelor in patients with possible Acute Coronary Syndrome (ACS)

Patient admitted with possible ACS (Not STEMI)

All patients receive Clopidogrel including a loading dose (300mg loading, 75mg daily maintenance) whilst awaiting Troponin and cardiologist review

Confirmed diagnosis following troponin results and Cardiology review

Confirmed diagnosis of NSTEMI
- Switch to Ticagrelor (Load with 180 mg then 90mg bd maintenance dose)
- Discharge with a maintenance dose of Ticagrelor 90mg bd for 12 months

Confirmed diagnosis of Unstable Angina
- Continue with Clopidogrel 75mg daily
- Discharge with a maintenance dose of Clopidogrel for 12 months
Contraindications and precautions...

<table>
<thead>
<tr>
<th></th>
<th>No CON/SWP to any P2Y12 inhibitor</th>
<th>At least 1 CON/SWP to any P2Y12 inhibitor</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>2 (0.4)</td>
<td>15 (1.9)</td>
<td>0.04</td>
</tr>
<tr>
<td>Death</td>
<td>0 (0)</td>
<td>9 (1.2)</td>
<td>0.03</td>
</tr>
<tr>
<td>MI</td>
<td>0 (0)</td>
<td>3 (0.4)</td>
<td>0.3</td>
</tr>
<tr>
<td>Urgent revascularization</td>
<td>2 (0.4)</td>
<td>2 (0.3)</td>
<td>0.6</td>
</tr>
<tr>
<td>Stroke</td>
<td>0 (0)</td>
<td>1 (0.1)</td>
<td>1.0</td>
</tr>
<tr>
<td>Bleeding BARC any type</td>
<td>93 (20.5)</td>
<td>113 (14.6)</td>
<td>0.009</td>
</tr>
<tr>
<td>BARC type 1</td>
<td>86 (18.9)</td>
<td>101 (13.1)</td>
<td>0.007</td>
</tr>
<tr>
<td>BARC type 2</td>
<td>5 (1.1)</td>
<td>7 (0.9)</td>
<td>0.8</td>
</tr>
<tr>
<td>BARC type ≥3</td>
<td>2 (0.4)</td>
<td>5 (0.6)</td>
<td>1.0</td>
</tr>
</tbody>
</table>
Fig. 2. Appropriateness of overall P2Y12 inhibitor selection initially and at discharge.
Fig. 3. Appropriateness of each P2Y12 inhibitor selection initially and at discharge.
<table>
<thead>
<tr>
<th></th>
<th>Prasugrel/ticagrelor treated N = 269</th>
<th>Switched from clopidogrel to ticagrelor/prasugrel N = 269</th>
<th>P</th>
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</tr>
<tr>
<td>Bleeding BARC type 3</td>
<td>4 (1.5)</td>
<td>9 (3.3)</td>
<td>0.3</td>
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<td>Bleeding BARC any type</td>
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<tr>
<td>MACE</td>
<td>6 (2.2)</td>
<td>4 (1.5)</td>
<td>0.8</td>
</tr>
</tbody>
</table>
Clopidogrel on top of ASA Efficacy and Safety Profile Has been Established in More than 100,000 Patients

Indication in patients after MI, IS, or with established PAD

Indication in UA/NSTEMI patients

Publication Date

CURE: Magnitude of Benefit

- **Primary Outcome:**
  - MI, stroke or CV death: 11.4% placebo,
  - 9.2%** clopidogrel (22 per 1000 absolute difference)
  - (Non-CV death 0.7 vs 0.7%)

**NNT = 48** Treating 100 patients for 9-12 months: prevents 2 CV deaths/MI/IS

**NNH = 99** i.e. 1 major bleeding event

TIMI bleeding criteria: 68 clopidogrel, 73 placebo RR 0.94 (CI 0.68-1.30)
GUSTO criteria: 78 clopidogrel, 70 placebo RR 1.11 (CI 0.81-1.55)
Ok Doc, newer antiplatelets but for how long?
Only prospective randomized studies comparing **two different durations** can answer the above question reliably…

- Such studies **are lacking** with clopidogrel **in ACS**
- Such studies **are lacking** with newer antiplatelet agents (prasugrel-ticagrelor)
How to determine optimal duration of DAPT

Prospective studies of a fixed duration comparing Tx...

- Prospective randomized studies comparing two different therapies for a fixed duration...
  - Indirectly suggest probable differences in effectiveness relative to duration of Tx...
    - Most studies with clopidogrel in ACS (e.g. CURE)
    - Few studies with prasugrel-ticagrelor
How to determine optimal duration of DAPT

Landmark analyses …

- Landmark analyses…
- Examine the effect of treatment after a fixed time point
  - Including only pts without events since this time point…
  - Ignoring cross-over following this time point
- Few such analyses available…
How to determine optimal duration of DAPT

Studies of Non-adherence

- Studies of DAPT non-adherence provide …
  - Direct evidence regarding:
    - Reasons of non-adherence…
    - Consequences of non-adherence…
  - Indirect evidence regarding optimal duration of DAPT

- Such studies are scarce with clopidogrel in ACS
- Such studies are lacking with newer antiplatelet agents (prasugrel-ticagrelor)
CURE: Impact of clopidogrel compared with placebo in CV death, MI, or stroke within first 30 ds and from 30 ds to 12 mos.

And the absolute difference continued to widen throughout the period of the study...

A subanalysis of pts from the CHARISMA trial found that those with prior MI experienced a 23% relative reduction in the composite end point of CV death, MI, or stroke with DAPT over 27.6 mos...

Continued divergence of the event curves at the end of the follow-up period suggests that the benefits of DAPT may be particularly enduring in this patient subgroup.

1.5% absolute reduction
**CHARISMA**

**Primary End Point**

<table>
<thead>
<tr>
<th>CV Death/MI/Stroke</th>
<th>Placebo, %</th>
<th>Clopidogrel, %</th>
<th>HR (95% CI &amp; CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior MI</td>
<td>8.3</td>
<td>6.6</td>
<td>0.774 (0.613-0.978)</td>
<td>0.031</td>
</tr>
<tr>
<td>Prior IS</td>
<td>10.7</td>
<td>8.4</td>
<td>0.780 (0.624-0.976)</td>
<td>0.029</td>
</tr>
<tr>
<td>Prior PAD</td>
<td>8.7</td>
<td>7.6</td>
<td>0.889 (0.571-1.125)</td>
<td>0.285</td>
</tr>
<tr>
<td>Entire cohort</td>
<td>8.8</td>
<td>7.3</td>
<td>0.829 (0.719-0.955)</td>
<td>0.010</td>
</tr>
</tbody>
</table>

DAPT for ACS following CURE…

- Benefit of 12 mo DAPT
  - @ Clopidogrel
- Continuing CV risk beyond 12 months
  - Role of extended DAPT Tx?
    - For all pts?
    - For high risk pts?
Primary efficacy (events prevented) and excess in life-threatening bleeding in clopidogrel group compared with placebo group.

There is going to be bleeding, and bleeding tends to be more common and larger in magnitude early on. That is probably a matter of self-selection or Darwinism…

Risk was pretty low for clopidogrel. Not zero, but the incremental risk over the low baseline risk with aspirin was rather small after about 6 to 9 months.

**CHARISMA**

**Instantaneous Hazard for Moderate or Severe Bleeding**

GUSTO Severe or Moderate Bleeding

N = 9478 patients with prior MI/stroke/PAD

- Placebo + aspirin
- Clopidogrel + aspirin

**Instantaneous hazard analysis:** looks at pts who are tolerating Tx at a particular time point and seeing what their hazard is…

Conclusion-1a

- Indirect evidence that ACS pts might benefit from extended DAPT Tx with clopidogrel...
- Bleeding may not be a concern at long term...
Looking at the Ok Doc problem in a different way…

- *Five years ago* if you had a pt, **with DM** who had **3 stents for an ACS** and had actually taken 1 year of DAPT, and he or she came to you in the office and said: "Doctor, I am doing great. Do I still have to take my *clopidogrel*?"

- Well, **not bleeding**; doing great; has had it for a year…

- How many of you would stop the DAPT?
If you have a pt, with DM who has 3 stents for an ACS and has actually taken 1 year of DAPT, and he or she comes to you in the office and says:

- “Doctor, I am doing great. Do I still have to take my prasugrel-ticagrelor?”

- Well, she is not bleeding; she is doing great; he or she has had it for a year…

- Are you going to stop the DAPT?
The guidelines...
Class-I 12 months therapy with...

- **Ticagrelor 180/90 mg** regardless of Tx strategy, including Clopidogrel pretreated pts

- **Prasugrel 60/10 mg** in P2Y12 naïve pts, planned for PCI, unless high risk of bleeding (no-stroke/TIA)

- **Clopidogrel 300/600/75 mg** recommended only if newer agents unavailable or contraindicated...

- Double Clopidogrel for 7 days in PCI pts without risk of bleeding (IIa)

- Ticagrelor or Clopidogrel post-CABG (IIa)
### STEMI

<table>
<thead>
<tr>
<th>Class-I</th>
<th>12 months therapy with...</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Ticagrelor 180/90 mg with no restriction</td>
<td></td>
</tr>
<tr>
<td>- Prasugrel 60/10 mg in clopidogrel naïve pts, if &lt;75 yrs, no-stroke/TIA</td>
<td></td>
</tr>
<tr>
<td>- Clopidogrel 300/600/75 mg recommended only if newer agents unavailable or contraindicated...</td>
<td></td>
</tr>
</tbody>
</table>

**pPCI**

- Ticagrelor & Prasugrel post-fibrinolysis: Class-III
DAPT duration after an ACS

- **UA/NSTEMI pts**
  - Up to 12 months if treated conservatively
  - At least 12 months if treated with PCI

- **STEMI pts**
  - 12 months or longer in pts with undergoing pPCI with BMS and DES

2012 ACC AHA Guidelines
Antiplatelet Therapy to Support Primary PCI for STEMI

A loading dose of a P2Y$_{12}$ receptor inhibitor should be given as early as possible or at time of primary PCI to patients with STEMI. Options include:

- Clopidogrel 600 mg; or
- Prasugrel 60 mg; or
- Ticagrelor 180 mg

P2Y$_{12}$ inhibitor therapy should be given for 1 year to patients with STEMI who receive a stent (BMS or DES) during primary PCI using the following maintenance doses:

- Clopidogrel 75 mg daily; or
- Prasugrel 10 mg daily; or
- Ticagrelor 90 mg twice a day

O’Gara et al. JACC; 2013:e78–140

Patras University Hospital
Antiplatelet Therapy for Secondary Prevention in the First Year Following PCI: ACS AND PCI

We suggest continuation of a P2Y₁₂ inhibitor with ASA beyond 12 months be considered in patients with a high thrombosis risk and a low bleeding risk
(Weak Recommendation, Low Quality Evidence)

We suggest against switching the P2Y₁₂ inhibitor initially selected at discharge unless there is a compelling clinical reason (e.g. stent thrombosis, bleeding, or cardiovascular event)
(Weak Recommendation, Very Low Quality Evidence)
Recommendations of **DAPT duration** after an **ACS event** is based on **consensus data** rather than **clinical-trial data**.
What is the evidence for extended DAPT Tx in the era of newer antiplatelet agents?
The curves in PLATO and TRITON seem to continue to diverge...

**PLATO**
- Clopidogrel
- Ticagrelor

**TRITON-TIMI 38**
- Clopidogrel
- Prasugrel

HR = 0.80
P = .003

---

PLATO: Primary efficacy endpoint over time (composite of CV death, MI or stroke)

0–30 days

RRR of 12%

Days after randomisation

Cumulative incidence (%)

(HR=0.88; 95% CI=0.77–1.00; p=0.045)

Days after randomisation

31–360 days

RRR of 20%

No. at risk

Ticagrelor 9333

Clopidogrel 9291

8942 8827 8763

8875 8763 8688

8673 8543 8397 7028 6480 4822

8688 8437 8286 6945 6379 4751
Ticagrelor Benefit Maintained Throughout Year

1st 30 days

Kaplan-Meier Estimated Rate (%)

- Ticagrelor (443 / 9333)
- Clopidogrel (502 / 9291)

From Randomization to:

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>ARR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 30</td>
<td>0.88</td>
<td>0.6</td>
</tr>
<tr>
<td>Day 60</td>
<td>0.84</td>
<td>1.0</td>
</tr>
<tr>
<td>Day 90</td>
<td>0.86</td>
<td>1.0</td>
</tr>
<tr>
<td>Day 120</td>
<td>0.86</td>
<td>1.1</td>
</tr>
<tr>
<td>Day 180</td>
<td>0.85</td>
<td>1.3</td>
</tr>
<tr>
<td>Day 360</td>
<td>0.84</td>
<td>1.9</td>
</tr>
</tbody>
</table>

No. at risk

- Ticagrelor 9333
  - Day 0: 8942
  - Day 15: 8827
  - Day 30: 8763
- Clopidogrel 9291
  - Day 0: 8875
  - Day 15: 8763
  - Day 30: 8688

Patras University Hospital
First and recurrent ischaemic events reduced with ticagrelor vs. clopidogrel

number needed to treat = 54

CV death, MI or stroke (number of events)

Ticagrelor

- First events: 868
- Additional events: 189

Clopidogrel

- First events: 1020
- Additional events: 205

p = 0.003

n = 1225

n = 1057

*p = 0.40; †p = 0.002.

CV, cardiovascular; MI, myocardial infarction.

First and recurrent PLATO major bleeding events were similar with ticagrelor and clopidogrel.

Recurrence bleeding events tended to be infrequent.

- Ticagrelor: First events: 961, p=0.43
- Ticagrelor: Additional events: 70, p=0.89
- Clopidogrel: First events: 929, p=0.43
- Clopidogrel: Additional events: 68, p=0.53

The landmark analysis of the rate of MI in the overall TRITON-TIMI 38 study population.

Results driven by reduction in MI...
Conclusion-2

- Direct evidence that the longer the ticagrelor based DAPT up to 12 mo, the more the benefit...
- Indirect evidence that certain pt populations (e.g. ACS) might benefit from extended DAPT Tx (>12 mo) with newer agents...
- Bleeding is a concern, but is it really at long term?
# New Trials With Ticagrelor

<table>
<thead>
<tr>
<th>Trial</th>
<th>Title</th>
<th>Duration</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEGASUS-TIMI 54</td>
<td>A Randomised, Double-Blind, Multinational Study to Prevent Major Vascular Events With Ticagrelor Compared to Aspirin (ASA)</td>
<td>90 days</td>
<td>Stroke or TIA</td>
</tr>
<tr>
<td>EUCLID</td>
<td>A Randomized, Double-blind, Parallel Group, Multicentre Phase IIIb Study to Compare Ticagrelor With Clopidogrel Treatment on the Risk of Cardiovascular Death, Myocardial Infarction and Ischemic Stroke in Patients With Established Peripheral Artery Disease (EUCLID Examining Use of ticagrelor In pad)</td>
<td>37 months</td>
<td>PAD</td>
</tr>
</tbody>
</table>
Does this mean that DAPT cessation within 12 mos following an ACS is harmful?
Data on hospitalizations, pharmacy prescription claims, and subsequent hospitalizations and deaths for 3.7 million individuals in Denmark...

29 268 pts with a first-time MI in a nationwide cohort
The risk was higher for patients with a STEMI as the index MI than for patients that had a non-STEMI as the index MI.

Multivariable adjusted Poisson analyses of the risk in the first 90 ds of discontinuation of clopidogrel treatment compared with the next 90 ds of discontinuation…
The risk of severe or fatal bleeding for medically treated pts decreases as time passes from the index MI. No difference in the risk of bleeding for pts who continue or discontinue Tx.
Indirect evidence that certain pt populations (e.g. ACS @ PCI) might benefit from extended DAPT Tx with clopidogrel...

Bleeding may not be a concern at long term...

Non-adherence to clopidogrel based DAPT within 12 mo following an ACS leads to ischemic events...
2-fold increase in the risk of death or MI in the 0- to 90-day interval after clopidogrel cessation compared with later time intervals and compared with pts remaining on clopidogrel therapy…

Increased platelet prothrombotic activity after clopidogrel withdrawal rather than a stent-specific mechanism…

Bleeding events around the time of clopidogrel cessation…
Major Issue: Ensure patient’s adherence to DAPT at least for 12 months post-ACS until other evidence appears…
Discontinuation of clopidogrel and statin prescribing in primary care following NSTEMI or STEMI

Patients in linked MINAP-GPRD dataset
- Linked Dataset: 23,740
- NSTEMI/STEMI: 7,543
  Aged ≥40, discharged from hospital to home after 2003
- Clopidogrel prescription in 1° care: 4,650 within 3 months of Acute MI

**ADJUSTED ODDS OF PRESCRIPTION AT 1 YEAR**

**CLOPIDOGREL**
- NSTEMI: 0.53 (0.51-0.55)
- STEMI: 0.54 (0.52-0.56)

**STATINS**
- NSTEMI: 0.84 (0.82-0.85)
- STEMI: 0.89 (0.87-0.90)

**Under-use of evidence-based treatment**
Discontinuation of clopidogrel and statin prescribing in primary care following NSTEMI or STEMI

Characteristics associated with discontinuation of 1° care clopidogrel prescribing within 1 year

adjusted for gender, alcohol, diabetes, smoking, BMI, SES, history of angina/MI, prior aspirin, prior hospitalisations, geographical region

<table>
<thead>
<tr>
<th>INTERVENTION</th>
<th>None</th>
<th>PCI</th>
<th>0.72 (0.63-0.83)</th>
<th>CABG</th>
<th>1.82 (0.99-3.35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE</td>
<td>Age 40-49</td>
<td>Age 50-59</td>
<td>1.13 (0.88-1.45)</td>
<td>Age 60-69</td>
<td>1.36 (1.07-1.74)</td>
</tr>
<tr>
<td>BLEEDING</td>
<td>None</td>
<td>Bleed</td>
<td>1.34 (1.03-1.73)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Characteristics associated with death or MI in first year after discharge

adjusted for age, gender, discharge diagnosis, socioeconomic status, medical history of angina/AMI, calendar year and geographical region

<table>
<thead>
<tr>
<th>AMI PHENOTYPE</th>
<th>NSTEMI</th>
<th>STEMI 0.72 (0.63-0.82)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>AGE</th>
<th>Age 40-49 0.84 (0.58-1.17)</th>
<th>Age 50-59 1.08 (0.78-1.50)</th>
<th>Age 60-69 1.60 (1.17-2.19)</th>
<th>Age ≥80 2.60 (1.91-3.54)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>SOCIOECONOMIC DEPRIVATION</th>
<th>0 (least deprived)</th>
<th>1 1.27 (1.04-1.56)</th>
<th>2 1.20 (0.98-1.47)</th>
<th>3 1.33 (1.08-1.63)</th>
<th>4 (most) 1.52 (1.23-1.86)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>CLOPIDOGREL PRESCRIBING</th>
<th>No prescribing</th>
<th>&lt;3 months 0.61 (0.52-0.72)</th>
<th>3-11 months 0.53 (0.44-0.65)</th>
<th>&gt;11 months 0.68 (0.50-0.92)</th>
</tr>
</thead>
</table>

Discontinued 1.45 (1.22-1.73)
Continued* Discontinued* 2.62 (2.17-3.17)

*these analyses restricted to those prescribed clopidogrel

Hazard ratio and 95% CI
GRAPE registry: 8 Greek Hospitals

Alexopoulos D., Xanthopoulou I. 2013

Patras University Hospital
### PARIS registry: Baseline Characteristics

Enrolled: n= 5033  
Complete 30 Day Follow-Up Available: 5023  (99.3%)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients (n=5033)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>63.96 ± 11.32</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>29.26 ± 5.63</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>3750 (74.5)</td>
</tr>
<tr>
<td>Acute coronary syndrome, n (%)</td>
<td>2047 (40.9)</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>984 (19.6)</td>
</tr>
<tr>
<td>Diabetes Mellitus, n (%)</td>
<td>1663 (33.0)</td>
</tr>
<tr>
<td>Insulin-requiring DM, n (%)</td>
<td>547 (10.9)</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>3810 (75.7)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>4020 (79.9)</td>
</tr>
<tr>
<td>Peripheral Vascular Disease, n (%)</td>
<td>396 (7.9)</td>
</tr>
<tr>
<td>Prior coronary artery disease, n (%)</td>
<td>1613 (32.1)</td>
</tr>
<tr>
<td>Prior MI, n (%)</td>
<td>1220 (24.2)</td>
</tr>
<tr>
<td>Prior PCI with stenting, n (%)</td>
<td>1853 (36.8)</td>
</tr>
<tr>
<td>Prior CABG, n (%)</td>
<td>691 (13.7)</td>
</tr>
<tr>
<td>Prior stroke, n (%)</td>
<td>174 (3.5)</td>
</tr>
</tbody>
</table>
Thienopyridine at Discharge

- Clopidogrel (n = 4647)
- Prasugrel (n = 315)
- Ticlopidine (n = 69)
At 2 years, 40% of patients were still on some DAPT!
Modes of Non-adherence

- **Discontinuation (Κατάργηση):** as per recommendation of their physician who felt subject no longer needed therapy.

- **Interruption (Προσωρινή Διακοπή):** on a voluntary basis and under guidance and recommendation of their physician due to **need for** surgery. DAPT will be **reinstituted within 14 days**.

- **Disruption (Διάρρηξη-Διάσπαση):** due to **bleeding or non-compliance**. Includes use of DAPT at lower dose levels than prescribed.
Rates of Non-Adherence (Patient-level)

Incidence of Non-Adherence
- Adherent (4929) - 98%
- Non-Adherent (104) - 2%

Non-Adherence by Mode
- Disruption (72) - 69%
- Interruption (20) - 19%
- Discontinuation (12) - 12%
Reasons for Disruption

Patras University Hospital

Mehran et al. ESC 2013
**PARIS: DAPT Cessation and MACE**

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>P</th>
<th>Events (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>On DAPT</td>
<td>1.00 (Ref)</td>
<td></td>
<td>413</td>
</tr>
<tr>
<td>Discontinuation</td>
<td>0.63 (0.46, 0.86)</td>
<td>.004</td>
<td>52</td>
</tr>
<tr>
<td>Interruption</td>
<td>1.41 (0.94, 2.12)</td>
<td>.101</td>
<td>26</td>
</tr>
<tr>
<td>Disruption</td>
<td>1.50 (1.14, 1.97)</td>
<td>.004</td>
<td>67</td>
</tr>
<tr>
<td>0-7 d</td>
<td>7.04 (3.31, 14.95)</td>
<td>&lt;.001</td>
<td>7</td>
</tr>
<tr>
<td>8-30 d</td>
<td>2.17 (0.97, 4.88)</td>
<td>.06</td>
<td>6</td>
</tr>
<tr>
<td>31+ d</td>
<td>1.30 (0.97, 1.76)</td>
<td>.083</td>
<td>54</td>
</tr>
</tbody>
</table>

*Cardiac death, def/prob ST, spontaneous MI, clinically driven TLR. All Cox Models adjusted for age, gender, region, ACS presentation, type of stent, and number of stents implanted.

Stent Thrombosis

Probable (n=9)

Definite (n=17)

Adherent (n=14)

Non-adherent (n=3)

Disrupted ASA (n=2)

Disrupted Clopidogrel (n=1)

Odds Ratio (95% CI) for stent thrombosis associated with non-adherence: 6.3 (1.9-21.4)
Oh, the patient has a stent. He probably needs to be on DAPT forever.
Conclusions

 12 mo of DAPT mandatory for all pts with ACS
 Maybe > 12 mo in ACS @ PCI
 No direct evidence @ prasugrel/ticagrelor
 The doctor is weighing the risk and benefit of DAPT duration...
 The doctor decides when to stop
 The doctor decides when to continue
 The doctor decides when to switch…
 But do we trust the doctor? And do we trust the patient?
Complex choice of drugs, and stents …

- **Opportunity:** Move away from the “one size fits all” model regarding DAPT choice/duration…

- Optimization of balance between thrombotic and bleeding risk

- Tailored DAPT treatment
Ronald Arbuthnott Knox (17 February 1888 – 24 August 1957) was an English priest and theologian. He was also a writer and a regular broadcaster for BBC radio.

Το καλό κύρηγμα πρέπει να ομοιάζει στη γυναικεία φούστα: Αρκετά βραχύ ώστε να διεγείρει το ενδιαφέρον, αλλά αρκετά μακρύ ώστε να καλύπτει τα απαραίτητα...

(Ronald Knox)
Patients with new onset NST-ASC or ST-ASC and registered in SWEDHEART 1 Jan 2006 to 1 Jul 2010 (N=56440)

Excluding patients such as those:
- Patients: with no clopidogrel dispensed, with clopidogrel use 180 days before the index event, treated with warfarin
- Patients experiencing death, re-infarction, stroke, bleeding, ST or coronary revascularization from discharge of the index event until day 111 (for the >3 vs 3 months comparison) or day 201 (for the >6 vs 6 months comparison)

SWEDHEART is a national registry of all pts hospitalized for ACS in Sweden

ACS= acute coronary syndrome, NSTE-ACS=non ST-elevation acute coronary syndrome, STE-ACS=ST-elevation acute coronary syndrome, ST=stent thrombosis, t=tablets, DAPT=dual antiplatelet treatment with clopidogrel and aspirin
No clear benefit of a longer treatment duration in the subgroup of pts that were not revascularized at the index event.
Importantly, while bleeding was statistically higher among pts taking longer-duration DAPT, the number of bleeding events was relatively low. In an analysis of events per 1000 person-years, 11 bleeds occurred in the more-than-three-months group vs 8 in the three-month DAPT group.
Defining High Risk Pts...

Capodanno et al, Clin Res Cardiol 2009

Risk factor  Score
Baseline LVEF < 50%  4
Acute coronary syndrome  3
Bifurcation lesion  2
LAD as treated vessel  2
≥ 2 DES implanted  2

Range  0-13

Cumulative Stent Thrombosis

Risk score  0  2  3  4  5  6  7  8  9  10  11  ≥ 11
No. at risk  64  157  82  137  208  92  197  45  223  15  122  35
Clopidogrel rebound phenomenon…

- **Clinical studies** of DAPT cessation in **stable pts** show conflicting results…
- **Platelet reactivity studies** in **stable stented pts** suggest that it does not exist
- **Clinical studies** of DAPT cessation in **ACS pts** suggest a relationship…
- **Platelet reactivity studies** in **ACS patients** are lacking…
### Relative Risk of Non-Adherence on 30 Day Stent Thrombosis in Contemporary Registries

<table>
<thead>
<tr>
<th>Registry</th>
<th>Adherent</th>
<th>Non-Adherent</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>PARIS Registry</td>
<td>0.5%</td>
<td>2.9%</td>
<td>5.8</td>
</tr>
<tr>
<td>Airoldi et al&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.9%</td>
<td>4.2%</td>
<td>4.7</td>
</tr>
<tr>
<td>eSELECT Registry&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.5%</td>
<td>4.6%</td>
<td>9.2</td>
</tr>
</tbody>
</table>

Procedural Information

Number of Stents

- One (n = 2792)
- Two (n = 1417)
- > Two (n = 824)
- 56%
- 28%
- 16%

Stent Type

- BMS alone (n = 817)
- DES alone (n = 4141)
- BMS & DES (n = 70)
- 82%
- 16%
- 2%
Non-Adherence guided by healthcare professionals

Recommended By

- Cardiologist (n = 31)
- Primary Care Physician (n = 15)
- ER Physician (n = 11)
- GI Specialist (n = 4)
- Other (n = 8)
- Unknown (n = 13)

Total episodes of “Recommended” DAPT non-adherence: 82
Reasons for Interruption

- **Aspirin**
  - Surgery: 34%
  - Allergy: 20%
  - GI Upset: 20%
  - Other Medical Procedure: 13%
  - Coumadin: 13%

- **Thienopyridine**
  - Surgery: 42%
  - Allergy: 33%
  - Other Medical Procedure: 25%

**Other Medical Procedure**
- **Surgery** (epidural, catheter removal, GI Scope)
  - ASA: 5
  - Thienopyridine: 5
  - GI Upset: 3
  - Allergy: 3
  - Coumadin: 2

*Patras University Hospital*
Difference in the risk related to discontinuation explained by PCI-related implantation of stents…

Existence of a 'rebound phenomenon' resulting in a transient increased risk of adverse CV events immediately after the discontinuation of clopidogrel treatment independent of PCI treatment?

- However not evident in medically treated pts…
- Pts undergoing PCI with stent implantation could be more susceptible to such a phenomenon?
Interplay between ticagrelor and adenosine in humans including impact on the heart, lungs, and brain (top); intestine (middle); platelets, kidneys, and liver (bottom).

Serebruany V L, and Atar D Eur Heart J
2009;eurheartj.ehp545

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The timing of benefit in PLATO looks ideal for long-term therapy. Unlike some other trials, the benefit after ticagrelor is somewhat delayed, growing slowly, but constantly over the entire time of the trial. The largest outcome benefit is observed at the end of the follow-up, ultimately justifying a chronic treatment regimen with ticagrelor. Importantly, since both pre-treatment and an adequate loading dose of clopidogrel have been permitted in
Variation in Response to Antiplatelet Therapy

Treatment Failure
- Complex Biologic Processes
  - Poor Compliance
- Inadequate Response On Lab Test
  - Bleeding Time
  - LTA, PFA-100
  - Ultegra, Flow Cytom., VASP, VerifyNow

Resistance
- Inadequate Biologic Response
Ερώτηση-1

- Ποιό από τα παρακάτω είναι σωστό

  A. Η πρασουγρέλη και η τικαγκρελόρη είναι αντιστρεπτοί αναστολείς του P2Y12 υποδοχέα

  B. Η τικαγκρελόρη στο STEMI δρα πιο γρήγορα από την πρασουγρέλη

  C. Ο συνδυασμός τικαγκρελόρης ή πρασουγρέλης με μπιβαλιρουδίνη απαγορεύεται λόγω αιμορραγιών

  D. Κανένα από τα παραπάνω
### Available P2Y<sub>12</sub> Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Inhibition of Platelet Aggregation to ADP*</th>
<th>Metabolism to Active Form</th>
<th>Time to Peak Effect</th>
<th>Consistency</th>
<th>Reversibility</th>
<th>Offset of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel 300 mg</td>
<td>~30%</td>
<td>2-step hepatic metabolism</td>
<td>4-6 h</td>
<td>+</td>
<td>Irreversible</td>
<td>~5 d</td>
</tr>
<tr>
<td>Clopidogrel 600 mg</td>
<td>~40%</td>
<td></td>
<td>~4 h</td>
<td>++</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prasugrel 60 mg</td>
<td>75%-80%</td>
<td>1-step hepatic metabolism</td>
<td>1-2 h</td>
<td>+++</td>
<td>Irreversible</td>
<td>~5 d</td>
</tr>
<tr>
<td>Ticagrelor 90 mg</td>
<td>75%-80%</td>
<td>Direct acting</td>
<td>1-2 h</td>
<td>+++</td>
<td>Reversible</td>
<td>1-2 d</td>
</tr>
</tbody>
</table>

*Data from multiple studies; no head-to-head comparisons of novel agents

Ερώτηση-2

- Γυναίκα 68 ετών με ΣΔ υποβάλλεται σε PCI @ DES λόγω ACS (Stent thrombosis). Ποιό από τα παρακάτω ίσως είναι καλύτερο?
  
  A. Η πρασουγρέλη
  
  B. Η τικαγκρελόρη
  
  Γ. Η κλοπιδογρέλη σε διπλάσια δόση (150 mg)
  
  Δ. Όλα ίδια είναι...
So far, there have been no large randomized trials directly comparing prasugrel and ticagrelor. ST rates were halved with prasugrel and cut by 27% with ticagrelor in their respective trials. Prasugrel benefits type 2 diabetes patients.
Ερώτηση-3

- Γυναίκα 79 ετών με ΣΔ, σοβαρή ΧΝΑ και STEMI, υποβάλλεται σε pPCI. Καταληλότερη αγωγή:
  - Α. Πρασουγρέλη 60 +10
  - Β. Τικαγκρελόρη 180 + 90 χ 2
  - Γ. Κλοπιδογρέλη 600 + 150 για 7 ημέρες
  - Δ. Κλοπιδογρέλη 600 + 75
  - Ε. Τα Β και Δ είναι αποδεκτά
Table 16  Doses of antiplatelet and antithrombin co-therapies

<table>
<thead>
<tr>
<th>Doses of antiplatelet co-therapies</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>With primary PCI</td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>Loading dose of 150–300 mg orally or of 80–150 mg i.v. if oral ingestion is not possible, followed by a maintenance dose of 75–100 mg/day.</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>Loading dose of 600 mg orally, followed by a maintenance dose of 75 mg/day.</td>
</tr>
</tbody>
</table>
| Prasugrel                         | Loading dose of 60 mg orally, followed by a maintenance dose of 10 mg/day.  
In patients with body weight <60 kg, a maintenance dose of 5 mg is recommended.  
In patients >75 years, prasugrel is generally not recommended, but a dose of 5 mg should be used if treatment is deemed necessary. |
| Ticagrelor                        | Loading dose of 180 mg orally, followed by a maintenance dose of 90 mg b.i.d. |
Table 18  Initial dosing of antithrombotic agents in patients with chronic kidney disease (estimated creatinine clearance <60 mL/min)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>No dose adjustment.</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>No dose adjustment.</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>No dose adjustment. No experience with end-stage renal disease/dialysis.</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>No dose adjustment. No experience with end-stage renal disease/dialysis.</td>
</tr>
</tbody>
</table>
**Table 10  Recommendations for the use of antithrombotic drugs in CKD**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel</td>
<td>No information in patients with renal dysfunction.</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>No dose adjustment necessary, including in patients with end-stage disease.</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>No dose reduction required; no information in dialysis patients.</td>
</tr>
</tbody>
</table>
PLATO: Ticagrelor in Elderly

CV, Death, MI, Stroke

HR, 0.89 (0.74-1.08)

P_{interaction} = .56

Non-CABG Major Bleeding

HR: 1.18 (0.87 - 1.59)

P_{interaction} = .96

KM Events at 12 Months, %

≥75 years (n=2878)
<75 years (n=15,744)

Clopidogrel: 300-600 mg load, 75 mg once/d
Ticagrelor: 180 mg load, 90 mg twice/d

Τι θα προτιμούσα εγώ;

Γυναίκα 79 ετών με ΣΔ, σοβαρή ΧΝΑ και STEMI, υποβάλλεται σε pPCI. Καταληλότερη αγωγή:

- Κλοπιδογρέλη 600 + 75

Special attention must be given to proper dosing of antithrombotics in elderly and renal failure patients.
Ερώτηση-4

Γυναίκα 60 ετών με STEMI, υποβάλλεται σε θρομβόλυση και πρόκειται να διακομιστεί για καθετηριασμό. Καταληλότερη αγωγή:

A. ASA + Πρασουγρέλη 60/10
B. ASA + Τικαγκρελόρη 180/90 x 2
G. ASA + Κλοπιδογρέλη 600/150 για 7 ημέρες
Δ. ASA + Κλοπιδογρέλη 300/75
E. Τα B και Δ είναι αποδεκτά
Oral or i.v. aspirin must be administered.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>Starting dose 150–500 mg orally or i.v. dose of 250 mg if oral ingestion is not possible.</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>Loading dose of 300 mg orally if aged ( \leq ) 75 years, followed by a maintenance dose of 75 mg/day.</td>
</tr>
</tbody>
</table>

Prasugrel and ticagrelor have not been studied as adjuncts to fibrinolysis and should not be given.
Ερώτηση-5

- Άσθενής με ΣΔ και ήπια ΧΝΑ μετά από ACS @ PCI (DES) παρουσιάζει ενδονοσοκομειακή εντερορραγία υπό ASA-τικαγκρελόρη. Καταληλότερη αγωγή:
  - Α. Διακοπή ASA-τικαγκρελόρης => ASA+Πρασουγρέλη 5 αργότερα
  - Β. Διακοπή ASA-τικαγκρελόρης => ASA+Τικαγκρελόρη
  - Γ. Διακοπή ASA-τικαγκρελόρης => ASA+Κλοπιδογρέλη 75 αργότερα
  - Δ. Όλα τα παραπάνω είναι αποδεκτά
ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

<table>
<thead>
<tr>
<th>Interruption and/or neutralization of both anticoagulant and antiplatelet therapies is indicated in case of major bleeding, unless it can be adequately controlled by specific haemostatic measures.</th>
<th>I</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interruption of antiplatelet drugs and neutralization of their activity with platelet transfusion is recommended, depending on the drugs under consideration and the severity of bleeding.</td>
<td>I</td>
<td>C</td>
</tr>
</tbody>
</table>
PARIS: Modes of DAPT Cessation

- **Discontinuation**
  - Patients discontinued DAPT per recommendation of their physician who felt the patient no longer needed therapy

- ** Interruption**
  - Patients interrupted DAPT use on a voluntary basis and as guided by a physician (e.g., for surgery)
  - DAPT was then reinstituted within 14 days

- **Disruption**
  - Patients disrupted DAPT use due to bleeding or noncompliance
PARIS: DAPT Cessation and MACE*

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>P</th>
<th>Events (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>On DAPT</td>
<td>1.00 (Ref)</td>
<td></td>
<td>413</td>
</tr>
<tr>
<td>Discontinuation</td>
<td>0.63 (0.46, 0.86)</td>
<td>.004</td>
<td>52</td>
</tr>
<tr>
<td>Interruption</td>
<td>1.41 (0.94, 2.12)</td>
<td>.101</td>
<td>26</td>
</tr>
<tr>
<td>Disruption</td>
<td>1.50 (1.14, 1.97)</td>
<td>.004</td>
<td>67</td>
</tr>
<tr>
<td>0-7 d</td>
<td>7.04 (3.31, 14.95)</td>
<td>&lt;.001</td>
<td>7</td>
</tr>
<tr>
<td>8-30 d</td>
<td>2.17 (0.97, 4.88)</td>
<td>.06</td>
<td>6</td>
</tr>
<tr>
<td>31+ d</td>
<td>1.30 (0.97, 1.76)</td>
<td>.083</td>
<td>54</td>
</tr>
</tbody>
</table>

Hazard Ratio

*Cardiac death, def/prob ST, spontaneous MI, clinically driven TLR. All Cox Models adjusted for age, gender, region, ACS presentation, type of stent, and number of stents implanted.

Ερώτηση-6

- Άνδρας με ΚΜ υπό Sintrom και STEMI, υποβάλλεται σε pPCI (BMS) Καταληλότερη αγωγή:
  - A. ASA + Πρασουγρέλη 60/10 + OAC
  - B. ASA + Τικαγκρελόρη 180/90 χ 2 + OAC
  - G. ASA + Κλοπιδογρέλη 600/150 για 7 ημέρες + OAC
  - D. ASA + Κλοπιδογρέλη 300/75 + OAC
  - E. Κλοπιδογρέλη 300/75 + OAC
Prasugrel and ticagrelor have not been studied as adjuncts to OAC and should not be given.
WOEST: Less Bleeding With No Aspirin

- **Any TIMI Bleeding**
  - Double Therapy: 19.5
  - Triple Therapy: 44.9
  - P < .001
  - HR = 0.36 (0.26-0.50)

- **Death, MI, TVR, Stroke, ST**
  - Double Therapy: 11.3
  - Triple Therapy: 17.7
  - P = .025
  - HR = 0.60 (0.38-0.94)

N = 563 patients on OAC who underwent stenting
Double = OAC + clopidogrel (75 mg); triple = OAC + clopidogrel + aspirin (80 mg)

### PLATO: Ticagrelor vs Clopidogrel by Aspirin Dose

<table>
<thead>
<tr>
<th>Region</th>
<th>Aspirin Dose (mg)</th>
<th>Ticagrelor</th>
<th>Clopidogrel</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>E</td>
<td>N</td>
<td>E</td>
</tr>
<tr>
<td>US</td>
<td>≥300</td>
<td>324</td>
<td>40</td>
<td>352</td>
</tr>
<tr>
<td></td>
<td>&gt;100-&lt;300</td>
<td>22</td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>≤100</td>
<td>284</td>
<td>19</td>
<td>263</td>
</tr>
<tr>
<td>Non-US</td>
<td>≥300</td>
<td>140</td>
<td>28</td>
<td>140</td>
</tr>
<tr>
<td></td>
<td>&gt;100-&lt;300</td>
<td>503</td>
<td>62</td>
<td>511</td>
</tr>
<tr>
<td></td>
<td>≤100</td>
<td>7449</td>
<td>546</td>
<td>743</td>
</tr>
</tbody>
</table>

N = # patients  
E = # events

---

GLOBAL LEADERS

16,000 All-Comer Patients With PCI

PCI With BioMatrix Flex Stent*

Aspirin/ticagrelor for 1 mo followed by 23 mo ticagrelor monotherapy

Aspirin/ticagrelor (ACS) or aspirin/clopidogrel (non-ACS) for 12 mo followed by 12 mo aspirin monotherapy

1º EP: All-cause mortality/MI
2º EP: Bleeding 5

*Not approved for use in the United States.

ClinicalTrials.gov.[10]
Ερώτηση-7

- Άσθενής 78 ετών με Ηχ γαστρορραγίας, μετά από PCI πρόκειται να λάβει ASA-κλοπιδογρέλη και PPI

- Α. Συνταγογραφούμε ομεπραζόλη/εσομεπραζόλη χωρίς πρόβλημα

- Β. Καλύτερα να λάβει παντοπραζόλη (CYP2C19 ουδέτερη)

- Γ. Καλύτερη επιλογή η ρανιτιδίνη

- Δ. Καλύτερα να λάβει πρασουγρέλη και PPI
# Editorial Comment

## Omeprazole

A Possible New Candidate Influencing the Antiplatelet Effect of Clopidogrel*

Paul A. Gurbel, MD, FACC,† Wei C. Lau, MD,‡ Udaya S. Tantry, PhD†

*Baltimore, Maryland; and Ann Arbor, Michigan*

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**Comment on:**

N = 124 stented patients on clopidogrel randomized to omeprazole (20 mg) or placebo tested via VASP-P

<table>
<thead>
<tr>
<th>Mean PRI</th>
<th>Placebo</th>
<th>Omeprazole</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>82.2</td>
<td>83.9</td>
<td></td>
</tr>
<tr>
<td>Day 7</td>
<td>39.8</td>
<td>51.4</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>PRI Variation, %</td>
<td>-43.3</td>
<td>-32.6</td>
<td>&lt; .0001</td>
</tr>
</tbody>
</table>

Gurbel PA, et al.[1]
Gilard M, et al.[2]
FDA and EMEA Statements

“Healthcare providers should re-evaluate the need for starting or continuing treatment with a PPI, including Prilosec OTC, in patients taking clopidogrel”

FDA. May 13, 2009

“The product information for all clopidogrel-containing medicines should be amended to discourage concomitant use of PPIs unless absolutely necessary”

EMEA. May 29, 2009
FDA Warning: PPIs and Clopidogrel

11/17/2009

• Concomitant use of omeprazole and clopidogrel should be avoided because of the effect on clopidogrel's active metabolite levels and anti-clotting activity.
• Separating the dose of clopidogrel and omeprazole in time will not reduce this drug interaction.

10/27/2010 Update

• With regard to PPI drug class, this recommendation applies only to omeprazole and not to all PPIs. Not all PPIs have the same inhibitory effect on the enzyme (CYP2C19) that is crucial for conversion of clopidogrel into its active form.

11/2012 Labeling Update

• Avoid concomitant use of esomeprazole/omeprazole with clopidogrel.
Potential PPI Interaction With Formation of Thienopyridine Active Metabolites

- **PPI interaction**
- **85% Inactive Metabolites**
- **Oxidation (Cytochrome P450)**
- **Hydrolysis (Esterases)**
- **Proton Pump Inhibitors**
  - **CYPs:** 3A, 2B6, 2C19
  - **Omeprazole + esomeprazole inhibit CYP2C19**
  - **Pantoprazole does not**

**Clopidogrel**
- **85% Inactive Metabolites**
- **Oxidation (Cytochrome P450)**

**Prasugrel**
- **No PPI interaction**
- **Oxidation (Cytochrome P450)**

*Acute Coronary Syndromes*
COGENT: Omeprazole Had No Effect on CV Events in Prospective, Randomized Trial

Patients on aspirin (75-325 mg) randomly assigned to clopidogrel (75 mg) + placebo or clopidogrel (75 mg) combined with omeprazole (20 mg)

- Placebo
- Omeprazole

Events at 180 Days, n:

- Placebo: 55 events, n = 1885
- Omeprazole: 54 events, n = 1876

HR = 0.99 (0.68-1.44)
P = .98
COGENT: Omeprazole and Clopidogrel in a Prospective, Randomized Trial

Patients on aspirin (75-325 mg) randomly assigned to clopidogrel (75 mg) + placebo or clopidogrel (75 mg) combined with omeprazole (20 mg)

Gastroduodenal bleeding and UGIB HR = 0.13 (0.03 to 0.56)
All GI Events HR = 0.34 (0.18-0.63)

Bhatt DL, et al. [7]
Ερώτηση-8

- Άσθενής 78 ετών με Ηχ γαστρορραγίας, μετά από PCI πρόκειται να λάβει ASA-τικαγκρελόρη και PPI

- Α. Συνταγογραφούμε ομεπραζόλη/εσομεπραζόλη χωρίς πρόβλημα

- Β. Καλύτερα να λάβει παντοπραζόλη (CYP2C19 ουδέτερη)

- Γ. Καλύτερη επιλογή η ρανιτιδίνη

- Δ. Καλύτερα να λάβει πρασουγρέλη και PPI (Trilogy)
PLATO: Primary End Point by PPI Use

N = 18,599 (6539 on PPI; PPI use at physician discretion)

- **Clopidogrel**
  - No PPI: Adj HR 1.20 (1.04-1.35)
  - PPI: 10.9

- **Ticagrelor**
  - No PPI: Adj HR 1.24 (1.07-1.45)
  - PPI: 9.2

Clopidogrel = 300-600 mg LD, 75 mg MD
Ticagrelor = 180 mg LD, 60 mg BID MD

## PLATO: PPI Users Higher Baseline Risk

<table>
<thead>
<tr>
<th>Selected Baseline Characteristics</th>
<th>No PPI (n = 12,060)</th>
<th>PPI (n = 6539)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years</td>
<td>62</td>
<td>63</td>
</tr>
<tr>
<td>Age ≥ 75 years, %</td>
<td>14.7</td>
<td>16.8</td>
</tr>
<tr>
<td><strong>History, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>45</td>
<td>49.8</td>
</tr>
<tr>
<td>Chronic renal disease</td>
<td>3.8</td>
<td>5.1</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>5.8</td>
<td>6.8</td>
</tr>
<tr>
<td>Peptic ulcer</td>
<td>0.9</td>
<td>2.4</td>
</tr>
<tr>
<td>PCI</td>
<td>12.4</td>
<td>15.2</td>
</tr>
<tr>
<td>Coronary artery bypass graft surgery</td>
<td>5.4</td>
<td>6.9</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>6.2</td>
<td>4.6</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>5.3</td>
<td>6.8</td>
</tr>
<tr>
<td>Baseline hemoglobin, median</td>
<td>141</td>
<td>138</td>
</tr>
<tr>
<td><strong>TIMI Risk Score, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STEMI, TIMI Risk ≥ 3</td>
<td>43.3</td>
<td>47</td>
</tr>
<tr>
<td>NSTEMI, TIMI Risk ≥ 5</td>
<td>42.3</td>
<td>46.8</td>
</tr>
</tbody>
</table>

*All P < .05*

Ερώτηση-9

- Άσθενής 78 ετών με Ηχ ΑΕΕ, και γαστρορραγίας, μετά από PCI @ DES έλαβε ASA-κλοπιδογρέλη και PPI. Μετά από ένα έτος:
  
  A. Η ASA αυξάνει πολύ τον κίνδυνο αιμορραγίας. Καλύτερα να λάβει μόνο κλοπιδογρέλη έναντι ASA-PPI
  
  B. Η μονοθεραπεία με κλοπιδογρέλη έχει περισσότερες αιμορραγίες σε σχέση με ASA-PPI
  
  Γ. Δε χρήζει PPI
  
  Δ. Καλύτερα να λάβει πρασουγρέλη και PPI
  
  Ε. Τα B και Δ είναι αποδεκτά
ASA and Risk of GI Bleeding -- Meta-Analyses

- **Placebo**: 1 (Derry, BMJ 2000, 8 RCT in 1° / 2° prevention)
- **ASA 50-162 mg/d**: 1.59 (1.4-1.8) (Sanmuganathan, Heart 2001, 4 RCT in 1° prevention)
- **ASA 75-500 mg/d**: 1.69 (1.4-2.1) (Weisman, Arch Int Med 2002, 6 RCT in 2° prevention)
- **Placebo**: 1 (McQuaid, Am J Med 2006, 14 RCT in 2° prevention)
- **ASA 50-325 mg/d**: 2.5 (1.4-4.7)
- **ASA 75-325 mg/d**: 2.07 (1.6-2.7)

OR
GI Bleeding Increases Mortality

Pooled REPLACE-2, ACUITY, HORIZONS-AMI Patients

<table>
<thead>
<tr>
<th></th>
<th>No GI Bleed</th>
<th>GI Bleed</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 Days</td>
<td>1.1%</td>
<td>7.8%</td>
</tr>
<tr>
<td>1 Year</td>
<td>2.9%</td>
<td>16.4%</td>
</tr>
</tbody>
</table>

P < .0001

PPIs Reduce GI Complications in Patients on Aspirin

Patients with healed ulcer and *H. pylori*

- ASA 100 mg QD
- Randomized n = 123
- Lansoprazole (30 mg)
- Placebo
- Median 12 month f/u

Risk of Recurrent GI Ulcers, GI Bleed, or GI Complications

HR 10.6 (95% CI 1.3-86.1)

- Lansoprazole
  - 1.6%
- Placebo
  - 14.8%

Algorithm for Assessing GI Risk With Antiplatelet Therapy

- Need for antiplatelet therapy
  - Yes
  - Assess GI risk factors
    - Test for *H. pylori*; treat if infected
      - Yes
      - History of ulcer complication
        - History of ulcer disease (nonbleeding)
          - GI bleeding
          - Dual antiplatelet therapy
          - Concomitant OAC
          - More than 1 risk factor:
            - Aged ≥60 years
            - Corticosteroid use
            - Dyspepsia or GERD symptoms

- No
- Yes

PPI
Prevention of Recurrent GI Bleeding: Aspirin + PPI Better Than Clopidogrel Alone

Aspirin + esomeprazole vs clopidogrel in patients with prior GI bleeding and H pylori negative

- Esomeprazole + low-dose aspirin
- Clopidogrel alone

Chances of GI Bleeding at 12 Months,%

<table>
<thead>
<tr>
<th>Treatment</th>
<th>GI Bleeding at 12 Months</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin 80 mg + PPI 40 mg (n=159)</td>
<td>0.7%</td>
<td>.001</td>
</tr>
<tr>
<td>Clopidogrel (n=161)</td>
<td>8.6%</td>
<td></td>
</tr>
</tbody>
</table>

Chances of Cumulative Recurrent Ulcer at 52 Weeks

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cumulative Recurrent Ulcer at 52 Weeks</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin 100 mg + PPI 20 mg (n=86)</td>
<td>0%</td>
<td>.0019</td>
</tr>
<tr>
<td>Clopidogrel (n=84)</td>
<td>13.6%</td>
<td></td>
</tr>
</tbody>
</table>

Ερώτηση - 10

- Άνδρας με ΣΔ, 73 ετών, με μέτρια ΧΝΑ. Διάγνωση Ca προστάτου προς χ/γείο 3 μο μετά από ACS @ PCI (νεότερο DES) υπό πρασουγρέλη. Ιστορικό ST προ 2ετίας. Καταληλότερη στρατηγική:

  A. Αναβολή χ/γείου για 3 μήνες (αν επιτρέπεται) κ μετά διακοπή πρασουγρέλης

  B. Διακοπή πρασουγρέλης 7 ημέρες και χ/γείο => Επανέναρξη αργότερα στα 5 mg => 10 mg

  C. Διακοπή πρασουγρέλης 5 ημέρες => GPI-IV bridging => επανέναρξη πρασουγρέλης

  D. Διακοπή πρασουγρέλης 5 ημέρες => Κλοπιδογρέλη

  E. Τα A & Δ
80 year old man post pPCI for inferior STEMI, 43 days later interrupted a fixed combination of DAPT including ASA 100 mg and clopidogrel 75 mg o.d.

Θα προσδιορίζατε το PRU?
80 year old man post pPCI for inferior STEMI, 43 days later interrupted a fixed combination of DAPT including ASA 100 mg and clopidogrel 75 mg o.d.

PRU = 460. Τι θα δώσετε?
Timing of Benefit (Landmark Analysis)

Clopidogrel

Prasugrel

HR 0.82
P=0.01

HR 0.80
P=0.003

Wiviott SD et al. NEJM 2007;357:2001-15
Comparison of CURRENT and TRITON

At 30 days…

CV Death, MI or Stroke
↓ 21%

Definite Stent Thrombosis
↓ 51%

TIMI Major Bleed

CABG-related Bleeding

Fatal bleeding

---

B

% Intra Cranial Haemorrhage

% Fatal Bleeding

0.05 0.03
0.3 0.3
0.2
0.3

0.1 0.1
0.1

0.4

0.2
0.2

Clopidogrel x2 for one week
Prasugrel for 450 days
Ticagrelor for 360 days

---

Patras University Hospital
TRITON: Landmark analysis of time from first event to second event by randomized therapy.

The occurrence of a subsequent ischaemic event significantly reduced in the prasugrel group (HR 0.65, P = 0.016).

CV mortality following a non-fatal ischaemic event occurred significantly less frequently among pts treated with prasugrel (HR 0.46, 95% CI 0.25–0.82).