Reste t-il une place aux tests antiplaquettaires et génétiques ?

P. BARRAGAN. Ollioules, France
Déclaration de conflits d’intérêts

AUCUN
CLASSICS - clopidogrel versus ticlopidine after coronary stenting

Event rate at 28 days

Safety
(major bleed, neutropenia, thrombocytopenia, early drug discontinuation)

- Ticlopidine + ASA (n=340)
  - 9.1%

- Clopidogrel + ASA (n=680)
  - 4.5%

Efficacy
(Cardiac death, MI, TVR)

- Ticlopidine + ASA (n=340)
  - 0.9%

- Clopidogrel + ASA (n=680)
  - 1.3%

P = 0.005

NS
SAT at D+6: Plavix 75 + ASA 75/day
SAT at D+6: plavix 75 + ASA 75/day
SAT at D+6: plavix 75 x 1 + ASA 75
SAT at D+6: plavix 75 x 1 + ASA 75
Resistance to Thienopyridines: Clinical Detection of Coronary Stent Thrombosis by Monitoring of Vasodilator Stimulated Phosphoprotein Phosphorylation

Group 3: No SAT
Group 4: SAT

p < 0.0001

VASP

P. Barragan et al. AHA 2001
Mortalité après thrombose de stent

Wiviott et al. SCAI-ACCi2 2008

% Mortality

Stent thrombosis
N = 210

No stent thrombosis
N = 12,634

25.9%
HR 13.1
(95% CI 9.8 - 17.5)
P < 0.0001

2.6%
Le bon choix = bon équilibre risque de saignement vs réactivité plaquettaire récidivante
Plus d’événements si haute réactivité plaquettaire

Price MJ et al; Eur Heart J 2008
Mortalité plus haute à 2 ans après saignement
QUESTIONS :

1. Est-ce qu'une stratégie guidée peut nous aider à trouver ce juste équilibre?

2. Chez quels patients en particulier?
Elective or Urgent PCI with DES*

VerifyNow P2Y12 Test 12-24 hours post-PCI

PRU ≥ 230

Yes

High On-treatment Reactivity

N = 1109

High-Dose Clopidogrel†
clopidogrel 600-mg, then
clopidogrel 150-mg/day

No

Normal On-treatment Reactivity

N = 1105

Standard-Dose Clopidogrel†
clopidogrel 75-mg/day

Random Selection

N = 586

Standard-Dose Clopidogrel†
clopidogrel 75-mg/day

Primary Efficacy Endpoint: CV Death, Non-Fatal MI, Stent Thrombosis at 6 mo

Pharmacodynamics: Repeat VerifyNow P2Y12 at 1 and 6 months

*Peri-PCI clopidogrel per protocol-mandated criteria to ensure steady-state at 12-24 hrs
†placebo-controlled

All patients received aspirin (81-162mg daily)
Primary Endpoint @ 6 months: CV Death, MI, Stent Thrombosis

Observed event rates are listed; P value by log rank test.


Only 10% of patients with +TnI
Secondary Comparison @ 6 months: High vs. Not High Reactivity

Cumulative Incidence of CV death, non-fatal MI, or ST (%)

- High Residual Platelet Reactivity
- Not High Residual Platelet Reactivity

2.3% vs. 1.4%
HR 1.68 (CI 0.76, 3.72)
p = 0.20

No. at Risk
High Residual Reactivity 1105 1057 1028 1020 1015 1005 773 53
Not High Residual Reactivity 586 565 552 551 549 546 415 19
Successful PCI with DES without major complication and NO GPIIb/IIIa use

Post-PCI VerifyNow P2Y12 Assay (PRU)
2 - 7 hours after MD of clopidogrel 75 mg at day 1 post-PCI

Non-Responder

Yes

PRU > 208

No

Responder

A

N = 1075

“Prasugrel arm”
Prasugrel LD 60 mg
Prasugrel MD 10 mg QD
+ Clopidogrel placebo

B

N = 1075

“Clopidogrel arm”
Placebo LD
Clopidogrel MD 75 mg QD
+ Prasugrel placebo

C

N = 4350

“Standard Therapy”
Clopidogrel MD 75 mg QD

Non-interventional study (Registry)

N = 2,150 → 33%

Clinical Follow-up and blinded VerifyNow Assessment at 90 days, 180 days

Primary Endpoint: 6 month CV Death or MI
Disposition of patients in TRIGGER-PCI

ACS = 0 %

3,525 patients screened
3,492 VerifyNow testing
33 No test result

625 patients with PRU >208
2,658 pts. with PRU ≤208

202 patients declined

423 patients randomized

212 prasugrel
211 clopidogrel

210 received ≥1 dose prasugrel
210 received ≥1 dose clopidogrel

74 study discontinuations
15 Subject decision
1 Consent revoked
58 Early termination of study

73 study discontinuations
9 Subject decision
4 Consent revoked
60 Early termination of study

136 completed study
137 completed study
Summary of primary and secondary CEC-adjudicated efficacy endpoints

<table>
<thead>
<tr>
<th></th>
<th>Prasugrel (N=212)</th>
<th>Clopidogrel (N=211)</th>
<th>p</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days on study treatment (median)</td>
<td>174</td>
<td>174</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Primary composite efficacy EP:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV death or MI</td>
<td>0</td>
<td>1 (0.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Key secondary efficacy EPs:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>0</td>
<td>1 (0.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rehospitalization for cardiac ischemic event</td>
<td>2 (0.9%)</td>
<td>4 (1.9%)</td>
<td>0.992</td>
<td>0.99 (0.14-7.03)</td>
</tr>
<tr>
<td>Urgent TVR</td>
<td>2 (0.9%)</td>
<td>1 (0.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite ST</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>0</td>
<td>1 (0.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV death</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cause death</td>
<td>0</td>
<td>1 (0.5%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Non-CABG TIMI major, minor or minimal bleeding

Hazard Ratio 1.517
(95% CI, 0.428-5.376)
p=0.516

Event rate, %

Days from randomization

Prasugrel

Clopidogrel

Hazard Ratio 1.517
(95% CI, 0.428-5.376)
p=0.516
ARCTIC trial design

Coronary angiogram

VerifyNow P2Y12 + ASA

Drug (ASA, clopidogrel, prasugrel, GP2b3a I.) and Dose adjustments if high platelet reactivity

Stent-PCI

Drug and Dose adjustments if high platelet reactivity at Day 14

Standard of care

Stent-PCI

Standard of care

Primary endpoint at 12 months:
- Death, MI, stroke, stent thrombosis, urgent revascularization

12-month FU

73% elective, 27% stabilized NSTE-ACS, no STEMI

Statistical considerations:
- Assuming an annual risk of 9% and a 33% relative risk reduction (α risk at 5% and error β of 20%, bilateral test), 2,466 patients were necessary to demonstrate the superiority of the strategy of monitoring and adjustment.

## In-Lab monitoring and adjustment

<table>
<thead>
<tr>
<th></th>
<th>Conventional (n=1227)</th>
<th>Monitoring (n=1213)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aspirin poor responders - %</strong></td>
<td>NA</td>
<td>7.6</td>
</tr>
<tr>
<td>On-table aspirin loading in poor responders - %</td>
<td>NA</td>
<td>85</td>
</tr>
<tr>
<td><strong>Thienopyridine poor responders - %</strong></td>
<td>NA</td>
<td>35</td>
</tr>
<tr>
<td>On-table clopi. loading in poor responders - %</td>
<td>NA</td>
<td>80</td>
</tr>
<tr>
<td>On-table prasu. loading in poor responders - %</td>
<td>NA</td>
<td>3.3</td>
</tr>
<tr>
<td>On-table GP IIbIIIa loading in poor responders - %</td>
<td>NA</td>
<td>80</td>
</tr>
</tbody>
</table>

Predominant intervention after procedure: double-dose clopidogrel!
Primary Endpoint to 1 year

Death, MI, stroke, stent thrombosis, urgent revascularization

Endpoint driven by **periprocedural MI**, defined as Tn > 3x ULN 6hrs after procedure

- Conventional Monitoring: 34.6%
- Monitoring: 31.1%

HR = 1.13 [0.98-1.29]
p = 0.096
ANTARCTIC

**Trial design:** Patients with acute coronary syndrome undergoing stenting were randomized to tailored antiplatelet therapy (n = 435) versus conventional therapy (n = 442). All patients were started on prasugrel 5 mg daily.

**Results**
- CV death, MI, stroke, stent thrombosis, urgent revascularization, or bleeding at 1 year: 27.6% of the tailored therapy group versus 27.8% of the conventional therapy group (p = 0.98)
- CV death, MI, stent thrombosis, or urgent revascularization: 9.9% versus 9.3% (p = 0.80)

**Conclusions**
- Among elderly patients with acute coronary syndrome undergoing stenting, tailored antiplatelet therapy did not improve outcomes compared with conventional antiplatelet therapy
- Tailored antiplatelet therapy resulted in a large proportion of patients that were down-titrated to clopidogrel therapy

Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS): a randomised, open-label, multicentre trial

TROPICAL-ACS study, n=2610
HPR if Multiplate > 46 IU  
Sibbing et al, LANCET 2017
Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS): a randomised, open-label, multicentre trial

Non inferiority of guided de-escalation strategy on PEP

Sibbing et al, LANCET 2017
Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS): a randomised, open-label, multicentre trial

Trend for less bleeding with guided de-escalation strategy

Sibbing et al, LANCET 2017
Tropical ACS – subgroups analysis

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>( P_{\text{interaction}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACS presentation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STEMI ( n=1453 )</td>
<td>0.54 (0.35–0.83)</td>
<td>0.0116</td>
</tr>
<tr>
<td>NSTEMI ( n=1157 )</td>
<td>1.10 (0.77–1.58)</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men ( n=2052 )</td>
<td>0.78 (0.57–1.06)</td>
<td>0.60</td>
</tr>
<tr>
<td>Women ( n=558 )</td>
<td>0.92 (0.53–1.62)</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;70 years ( n=370 )</td>
<td>1.17 (0.69–2.01)</td>
<td>0.11</td>
</tr>
<tr>
<td>( \leq 70 ) years ( n=2240 )</td>
<td>0.70 (0.51–0.96)</td>
<td></td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes ( n=527 )</td>
<td>1.17 (0.71–1.93)</td>
<td>0.10</td>
</tr>
<tr>
<td>No ( n=2083 )</td>
<td>0.71 (0.52–0.99)</td>
<td></td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>0.81 (0.62–1.06)</td>
<td></td>
</tr>
</tbody>
</table>

Favours guided de-escalation  Favor control
Tests génétiques au "chevet" du patient

SpartanRX

the Verigene System
Estimated Rates of All Death + Nonfatal MI + Stroke, According to CYP2C19 Variant-Allele Polymorphisms


*2/*2  
*1/*1  
*1/*2

No. at Risk
<table>
<thead>
<tr>
<th></th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>No variant alleles</td>
<td>1572</td>
</tr>
<tr>
<td>1 Variant allele</td>
<td>576</td>
</tr>
<tr>
<td>2 Variant alleles</td>
<td>58</td>
</tr>
</tbody>
</table>

Adjusted P=0.003
### Les Essais en cours

<table>
<thead>
<tr>
<th>Essai</th>
<th>Groupes</th>
<th>Patients</th>
<th>Design</th>
<th>Statut</th>
</tr>
</thead>
<tbody>
<tr>
<td>GeCCO</td>
<td>ACS</td>
<td>14 600</td>
<td>Cohorte observ.</td>
<td>Arrêt prématuré</td>
</tr>
<tr>
<td>PAPI-2</td>
<td>PCI</td>
<td>7 200</td>
<td>Randomisé</td>
<td>Arrêt prématuré</td>
</tr>
<tr>
<td>TARGET-PCI</td>
<td>PCI</td>
<td>1 500</td>
<td>Randomisé</td>
<td>Arrêt prématuré</td>
</tr>
<tr>
<td>POPGenetics</td>
<td>PCI</td>
<td>2 700</td>
<td>Randomisé</td>
<td>Recrutement</td>
</tr>
<tr>
<td>TAILOR-PCI</td>
<td>PCI</td>
<td>5 200</td>
<td>Randomisé</td>
<td>Recrutement</td>
</tr>
<tr>
<td>ADAPT</td>
<td>PCI</td>
<td>700</td>
<td>Randomisé</td>
<td>Terminé</td>
</tr>
</tbody>
</table>
Thrombocyte Activity Reassessment and GENoTyping for PCI (TARGET-PCI)

Nonemergent PCI Patients (n = 1500)

Guided Therapy (n = 750)

On Clopidogrel Therapy

VerifyNow® P2Y\textsubscript{12} Guided Therapy†

- < 230 PRU: 75 mg MD Clopidogrel
- ≥ 230 PRU: 60 mg LD, 10/5 mg§ MD Prasugrel

Clopidogrel Naive

CYP 2C19 Guided Therapy‡

- *1/*1, *1/*17, 17/*17 or *2-*8/17: 600 mg LD, 75 mg MD Clopidogrel
- *1/*2-*8 or *2-*8/2-*8: 60 mg LD, 10/5 mg§ MD Prasugrel

Standard Therapy (n = 750)

2-wk Post-PCI VerifyNow Testing and Clinical Assessment, ≥ 230 PRU: Switch/Continue Prasugrel

3-mo VerifyNow Testing and Clinical Assessment, ≥ 230 PRU: Switch/Continue Prasugrel

6-Month VerifyNow Testing and Clinical Assessment

Primary Endpoint: 6-month CV death, nonfatal MI, ischemic stroke, and uTVR.
Secondary Endpoints: 1) Bleeding
2) Relation between CYP2C19 variants and PRU
3) Stability of PRU over 6 months
4) Relation of CYP2C19 variants and PRU to ischemia and bleeding

† ≥2 hours post-MD
‡ Baseline
§ Participants <60 kg or >75 years get 5 mg

Available at: http://clinicaltrials.gov/ct2/show/NCT01177592
Assessment of prospective CYP2C19 genotype guided Dosing of AntiPlatelet Therapy in Percutaneous Coronary Intervention (ADAPT)

The ADAPT study: A Pragmatic Randomized Clinical Trial

Genotyped → PCI → Usual care- no genotyping

Primary endpoint
Proportion of participants receiving prasugrel/ticagrelor

Secondary endpoints
1. Agreement with the genotype guided antiplatelet recommendations
2. Clinical Outcomes: Major Adverse Cardiac Events and Major Bleeding

ACC.18
Primary Outcome: Antiplatelet Drugs Prescribed

<table>
<thead>
<tr>
<th></th>
<th>Genotyped N=249</th>
<th>Usual Care N=255</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel</td>
<td>174 (70%)</td>
<td>201 (79%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Prasugrel or Ticagrelor</td>
<td>75 (30%)</td>
<td>54 (21%)</td>
<td></td>
</tr>
</tbody>
</table>

Fisher’s exact test
Assessment of prospective CYP2C19 genotype guided Dosing of AntiPlatelet Therapy in Percutaneous Coronary Intervention (ADAPT)

Prasugrel/ ticagrelor use greater in the LOF carriers

<table>
<thead>
<tr>
<th>Genotyped</th>
<th>Usual Care</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No-LOF</td>
<td>LOF carriers</td>
<td>N=255</td>
</tr>
<tr>
<td>N=174</td>
<td>n=68</td>
<td></td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>136 (78%)</td>
<td>201  (79%)</td>
</tr>
<tr>
<td></td>
<td>32 (47%)</td>
<td></td>
</tr>
<tr>
<td>Prasugrel or Ticagrelor</td>
<td>38 (22%)</td>
<td>54   (21%)</td>
</tr>
<tr>
<td></td>
<td>36 (53%)</td>
<td></td>
</tr>
</tbody>
</table>

P<0.001
Assessment of prospective CYP2C19 genotype guided Dosing of AntiPlatelet Therapy in Percutaneous Coronary Intervention Intervention (ADAPT)

### Clinical outcomes

<table>
<thead>
<tr>
<th></th>
<th>Genotyped (n=249)</th>
<th>Usual Care (n=255)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up time (months)</td>
<td>17.2 (7.5)</td>
<td>16.1 (8.2)</td>
<td>0.14</td>
</tr>
<tr>
<td>MACE</td>
<td>34 (13.7)</td>
<td>26 (10.2)</td>
<td>0.27</td>
</tr>
<tr>
<td>BARC 3 or 5 bleed</td>
<td>6 (2.4)</td>
<td>8 (3.1)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

MACE = myocardial infarction, stroke, death from cardiovascular cause, stent thrombosis, urgent revascularization
BARC = Bleeding Academic Research Consortium
CONCLUSIONS: Intérêt de l’utilisation routinière des tests de fonction plaquettaires et génétiques ?

1. Patients stables : aucun car faible taux d’événements

2. SCA : aucun si utilisation large des nouveaux P2Y12

3. Tests génétiques : aucune preuve clinique
   (la fonction CYP2C19 contribuant seulement dans 5 à 10 % à la réponse du clopidogrel)

4. Utiles: si une « désescalade » est envisagée
   30 000 tests fonctionnels/an seraient réalisés en France
Merci pour votre attention
## Current Status of RCTs of Platelet Function Testing in PCI

<table>
<thead>
<tr>
<th>Trial</th>
<th>Primary Endpoint</th>
<th>% biomarker positive</th>
<th>Intervention</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>GRAVITAS</td>
<td>D/MI/ST (after procedure)</td>
<td>10%</td>
<td>Clopidogrel 150mg</td>
<td>No benefit</td>
</tr>
<tr>
<td>TRIGGER</td>
<td>D/MI (after procedure)</td>
<td>0%</td>
<td>Prasugrel 10mg</td>
<td>No benefit</td>
</tr>
<tr>
<td>PCI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| ARCTIC    | D/MI/CVA/uTVR/ST (including periprocedural MI) | 27% “stabilized” NSTEACS (% biomarker positive not reported) | Recommended, but not required, personalized Rx Actual:  
- mostly GPI during procedure  
- mostly Clop 150mg post | No Benefit – Endpoint driven by elevation in TnI 6hrs post-PCI (approx 32% of patients) |

- Role of PFT in ACS not addressed
Why Not Prasugrel or Ticagrelor for All ACS Patients?

- Expensive
- Increased risk of bleeding
- Patients with low on-treatment reactivity (e.g., PRU<208), are at substantially lower risk of ischemic events compared with patients with higher reactivity
  - Absolute risk reduction will be lower (NNT higher) for patients with good response to clopidogrel
- Can PFT help us select the most appropriate patient for clopidogrel or a newer oral P2Y12 inhibitor?
Summary

- On-treatment reactivity (OTR) is a strong risk factor for post-PCI events

- Elective PCI patients in general have low event rates irrespective of OTR
  - More intensive inhibition with prasugrel or ticagrelor may increase bleeding more than reduce thrombotic events

- RCTs have not addressed “tailored” therapy in ACS
  - Can PFT identify patients who would benefit the least (or most) from ticagrelor or prasugrel – ie, help select the most appropriate oral P2Y\(_{12}\) antagonist?
  - Guidelines recommend against “routine” PFT

Price MJ. Lancet. 2013;382:583-584
Impact of High On-Aspirin Platelet Reactivity on Outcomes Following Successful DES Implant

ADAPT-DES: 8,526 all-comers patients who received dual antiplatelet therapy with aspirin and clopidogrel.

- Based on VerifyNow assay, high on-aspirin platelet reactivity (HAPR) found in 5.6% of patients
- HAPR was not associated with 2-year risks of MACE, stent thrombosis, MI, all-cause death, or bleeding
- Even in patients with clopidogrel resistance, which was itself tied to worse outcomes, HAPR was not related to adverse outcomes

**Conclusion:** HAPR is not commonly seen in patients who undergo successful PCI with a drug-eluting stent, and when it is found it does not seem to have a big impact on clinical outcomes.

GRAVITAS: Lower Reactivity Over Course of Trial Associated with Reduced With CV Death, MI, ST at 60 days

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR [95% CI]</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRU &lt;208</td>
<td>0.23 [0.05, 0.98]</td>
<td>0.047</td>
</tr>
<tr>
<td>ACS</td>
<td>3.95 [1.83, 8.53]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.49 [1.10, 5.64]</td>
<td>0.028</td>
</tr>
<tr>
<td>Stent Length (per mm)</td>
<td>1.01 [1.01, 1.02]</td>
<td>0.003</td>
</tr>
<tr>
<td>Prior MI</td>
<td>2.16 [0.94, 4.93]</td>
<td>0.068</td>
</tr>
<tr>
<td>Beta Blocker</td>
<td>1.27 [0.42, 3.85]</td>
<td>0.668</td>
</tr>
<tr>
<td>CrCl &lt;60</td>
<td>1.48 [0.69, 3.18]</td>
<td>0.668</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>1.76 [0.74, 4.16]</td>
<td>0.201</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>1.92 [0.87, 4.23]</td>
<td>0.108</td>
</tr>
</tbody>
</table>

*N=2796

*On-treatment reactivity treated as a time-varying covariate
CrCl = creatinine clearance, ACS = acute coronary syndrome, MI = myocardial infarction

Price MJ et al, Circulation 2011;124:1132-1137
Genotyping in daily practice?

Occurrence of CYP 2C19*2

- Whites: 30%
- Blacks: 40%
- East Asians: 55%

Patients at risk:

700,000 pts on 2,000,000 PCI/years