CYP2C19 *2 and *17 alleles have a significant impact on Platelet Response and Bleeding Risk in patients treated with Prasugrel

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Genetic Modulation of Clopidogrel Response

CYP2C19*2 loss-of-function allele

Stent Thrombosis

Impaired Response to clopidogrel

Frere et al, AJC 2008

Higher Rate of Ischemic Events

Hulot et al, JACC 2011
Genetic Modulation of Clopidogrel Response

CYP2C19*17 gain-of-function allele

Better Response to clopidogrel

Higher Rate of Bleeding Events

Frere et al, JTH 2008

Sibbing et al, Circulation 2010
Prasugrel and CYP2C19 variants?
CYPC19 variants and Prasugrel Response

Healthy Subjects, *17 variant not tested
Platelet testing after loading dose with LTA /ADP-Ag 20 µmol

Clopidogrel 300 mg (n=74)

Prasugrel 60 mg (n=71)

No significant Relationship between *2 and prasugrel response

Brandt et al, JTH 2007
CYPC19 variants and Prasugrel Response

Healthy Subjects, n=238, Active MB and LTA / ADP 20 µmol

Métabolite Actif

LTA ADP 20 µmol

No significant Relationship between *2 and prasugrel response

Mega et al, Circulation 2009
CYPC19 variants and Prasugrel Response

Healthy Subjects, n=238, Active MB and LTA / ADP 20 μmol

Active Metabolite

Pharmacokinetics

<table>
<thead>
<tr>
<th>Gene</th>
<th>% Difference in AUC_{0-t}</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19</td>
<td>-6.1</td>
<td>0.06</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>-5.3</td>
<td>0.27</td>
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<tr>
<td>CYP2B6</td>
<td>-0.4</td>
<td>0.90</td>
</tr>
<tr>
<td>CYP3A5</td>
<td>-0.8</td>
<td>0.82</td>
</tr>
<tr>
<td>CYP1A2</td>
<td>-3.5</td>
<td>0.47</td>
</tr>
</tbody>
</table>

Relative Percent Difference in AUC_{0-t} (95% CI) in Carriers vs. Non-Carriers of a Reduced-Function Allele

Mega et al, Circulation 2009
CYP2C19 variants et clinical outcome on prasugrel

TRITON study, ACS patients on prasugrel, n=1466, *17 not tested

No relationship between *2 and clinical outcomes

Mega et al, Circulation 2009
Limitations

- Biological response in healthy subjects
- No idea of impact of *17 on clinical events
- PT used was LTA, no idea with new test (VASP, bedside...)

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Objectives of the present study

Assess the influence of *2 et *17 alleles on:

- Prasugrel Response (PRI VASP) on 10 mg daily
- Incidence of HTPR (PRI VASP>50%)
- Incidence of ‘hyper-response ‘(< 25th percentile)
- Bleeding complications
Methods

- Single Center, Prospective study
- Consecutive ACS patients treated with prasugrel 10 mg/d
- Platelet Testing at one month on prasugrel with PRI VASP
- Genotyping for CYP2C19 *2 and *17 alleles
- BARC bleedings during one month FU
Results

- 213 patients included

- Baseline Characteristics: 45% STEMI, 30% DM

- Treatment: 100% ASA < 100 mg, 98% IPP
PRI VASP in the whole population

Mean PRI VASP = 29%

Incidence HTPR = 7%

n=15 (7%)

Mean = 29 +/- 14%
Influence of *2 allele on prasugrel response

**Impaired Response to Prasugrel in *2 Carriers**

- **PRI VASP**
  - *2 Carriers: 30%
  - *2 Non Carriers: 16%
  - p = 0.03

- **HTPR**
  - *2 Carriers: 15%
  - *2 Non Carriers: 4%
  - p = 0.01
Influence of *17 allele on prasugrel response

Better Response to Prasugrel in *17 Carriers

p=0.03

p=0.02
Definition of ‘hyper response’ to prasugrel

• Defined as PRI VASP < 25\textsuperscript{th} percentile

• PRI VASP < 17%

• 55/213 patients (26%)
Influence of *17 allele on prasugrel response

Higher Incidence of ‘hyper response’ in *17 carriers
Classification according to *2 et *17 alleles

• **Poor Metabolizers**
  (*2 carriers/*17 non carriers) (n=42)

• **Intermediate Metabolizers**
  (*2 carriers/*17 carriers and *2 non carriers/*17 non carriers) (n=107)

• **Ultrametabolizers**
  (*2 non carriers / *17 carriers) (n=64)
Classification and Prasugrel Response

PRI VASP (%)

- Poor Metabolizers
- Intermediate Metabolizers
- Ultra Metabolizers

p=0.005

Incidence of HTPR (PRI VASP>50%)

- Poor Metabolizers
- Intermediate Metabolizers
- Ultra Metabolizers

19%
6%
1%
p=0.002
Bleeding Complications

- 213 patients included

- At 1 month: 15% complications (n=32)

- 16 BARC 1
- 13 BARC 2
- 3 BARC 3
Relationship PRI VASP and Bleedings with Prasugrel

Lower PRI VASP in patients with bleeding complications

p=0.03

PRI VASP

No Bleeding

Bleeding

30%

24%
Relationship Hyper response and Bleedings (PRI VASP < 17%)

p=0.04

24% 12%

BARC Bleeding

Hyper Response
Other patients

Higher Bleeding Risk in prasugrel hyper responders
Relationship *17 Allele and Bleedings with Prasugrel

OR 2.5, p=0.02

Higher Bleeding Risk on prasugrel in *17 Carriers
Conclusion

• Influence of *2 and *17 alleles on prasugrel response

• Higher bleeding risk on prasugrel in *17 carriers
Perspectives

• Genotyping proposed to avoid clopidogrel in *2 carriers

• Genotyping to select candidates for new drugs?

  * Ultra Metabolizers → Clopidogrel?
  * Intermediate Metabolizers → Prasugrel?
  * Poor Metabolizers → Ticagrelor?

• Need validation in clinical studies