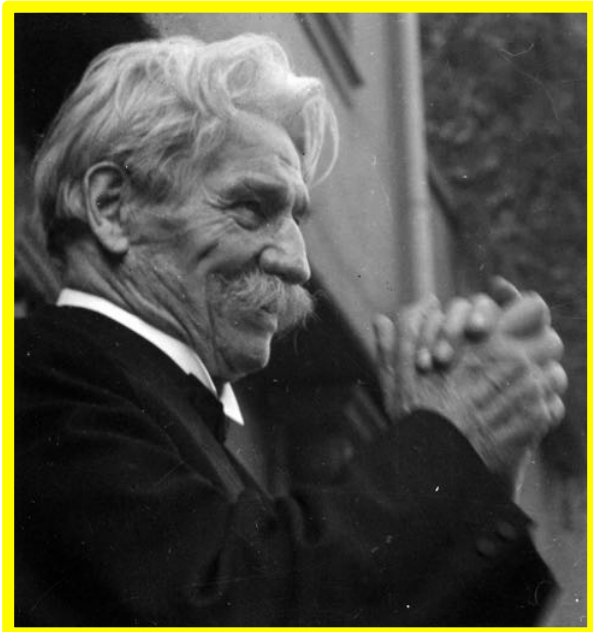


# SCA ST+ et Antiplaquettaires

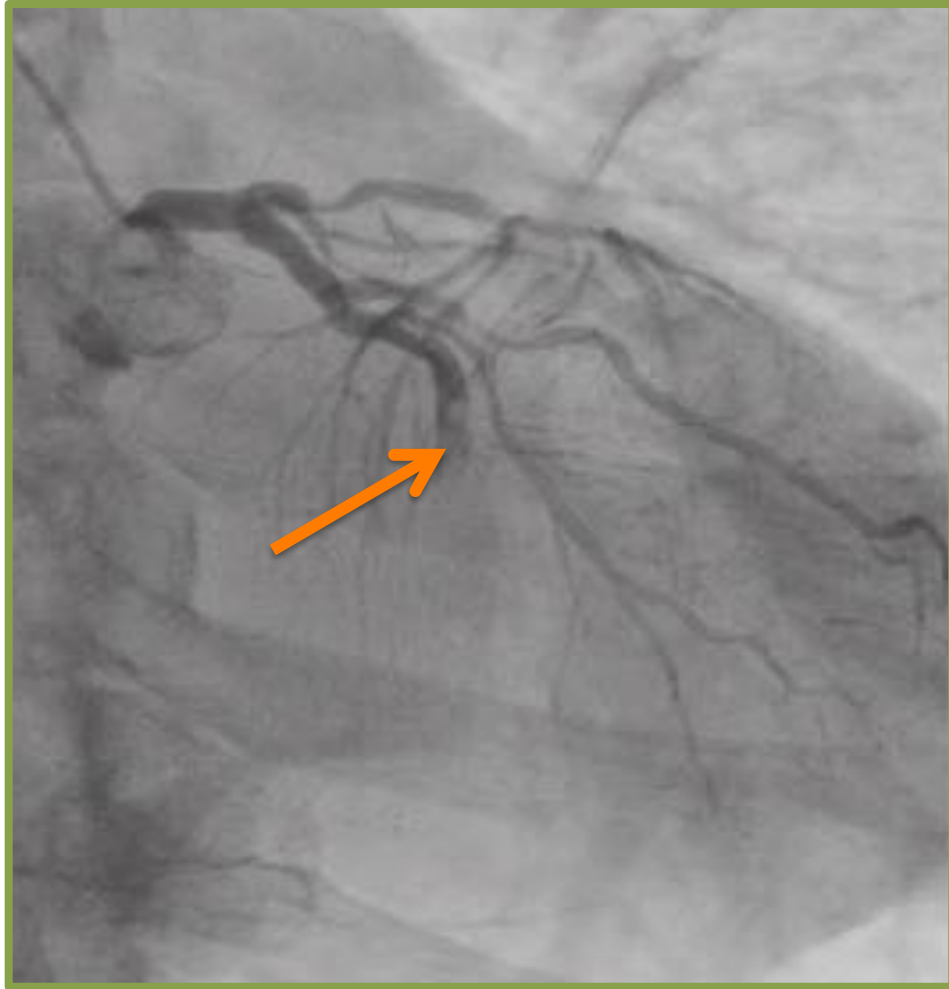
## Une Enigme ?

Docteur JP Monassier  
Hopital Albert Schweitzer  
Colmar



APPAC 2017





**ANTI-THROMBINES** **ANTI-PLAQUETTAIRES**

**HNF - HBPM - Bivalirudine**

## ANTI-PLAQUETTAIRES

◆ ASPIRINE 300 – 500 mg IV\*

◆ Anti-P2Y<sub>12</sub>

Clopidogrel  
Prasugrel  
Ticagrelor

◆ Anti GP IIb/IIIa

\* Recos : 162 – 325 mg voie orale

## Inhibiteurs Oraux du Récepteur Plaquettaire P2Y<sub>12</sub>

### ▪ THIENOPYRIDINES

▪ Clopidogrel : 600 mg / 75 mg



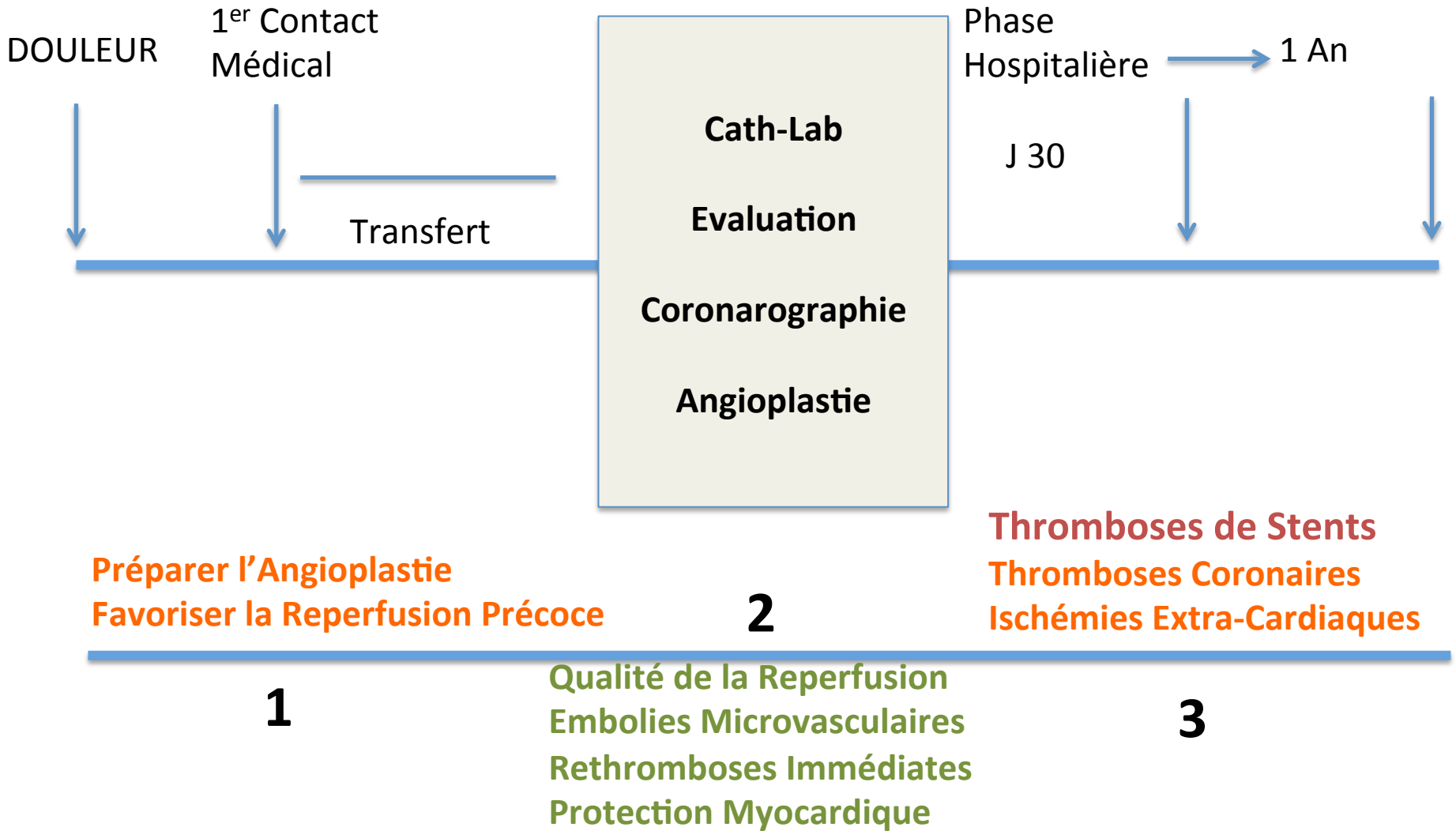
▪ Prasugrel : 60 mg / 10 mg

### ▪ DERIVE PYRIMIDIQUE

▪ Ticagrelor : 180 mg / 90 x 2 mg



◆ TOUT EN UNE MOLECULE !

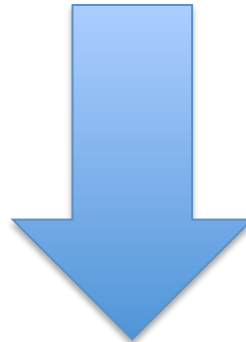


# ◆ « EVIDENCE BASED MEDICINE »

1 . DONNEES EXPERIMENTALES SOLIDES



2. TRANSLATION PERTINENTE VERS LA CLINIQUE



?

SCA ST+ DILATES

## Inhibiteurs Oraux du Récepteur Plaquettaire P2Y<sub>12</sub>

- **Volontaires Sains et Coronariens Stables**

- **Prasugrel\*** : 60 mg / 10 mg
- **Ticagrelor\*\*** : 180 mg / 90 x 2 mg



- ◆ **REPONSE BIOLOGIQUE SUPERIEURE**
- ◆ **REPONSE BIOLOGIQUE PLUS RAPIDE**
- ◆ **REPONSE BIOLOGIQUE CONSTANTE**

\*Pré-Métabolisme Hépatique Simple

\*\*Pas de Pré-Métabolisme Hépatique

**TRITON-TIMI 35 : Prasugrel**

**PLATO : Ticagrelor**

**Versus Clopidogrel – SCA ' s**

**N=32232**

**TRITON : SCA ST+ ACT**

**N=2438**

**PLATO : SCA ST+ ACT**

**N=4949**

**Anti-P2Y12 dose de charge avant la coronarographie**

Clopidogrel : **300 mg** (40 % 600 dans PLATO)

50 % Anti GP



Clopidogrel : **300** / 75 mg  
 Prasugrel : 80 / 10 mg

| Critère           | Prasugrel   | Clopidogrel | p    |
|-------------------|-------------|-------------|------|
|                   | 1235        | 1203        |      |
| <b>DCV/IM/AVC</b> | <b>8,2%</b> | <b>6,6%</b> | -    |
| DCV               | ?           | ?           |      |
| IM                | ?           | ?           | -    |
| AVC               | ?           | ?           | -    |
| Thr.Stent         | 1,1%        | 2,5%        | 0,01 |
| Décès             | ?           | ?           | -    |
| Hémorragies       | 1,2%        | 1,5%        | -    |

SCA ST+  
 ACT primaire :  
 69%

65%  
 ANTI GP

**J30**

◆ TRITON SCA ST+

Montalescot G Lancet 2009 ; 373 : 723-31

Clopidogrel : **300** / 75 mg  
 Prasugrel : 80 / 10 mg

| Critère           | Prasugrel   | Clopidogrel  | p    |
|-------------------|-------------|--------------|------|
|                   | 1235        | 1203         |      |
| <b>DCV/IM/AVC</b> | <b>9,9%</b> | <b>11,2%</b> | -    |
| DCV               | ?           | ?            |      |
| IM                | ?           | ?            | -    |
| AVC               | ?           | ?            | -    |
| Thr.Stent         | 1,5%        | 2,7%         | 0,05 |
| Décès             | ?           | ?            | -    |
| Hémorragies       | 3,1%        | 1,9%         | -    |

SCA ST+  
 ACT primaire :  
 69%

65%  
 ANTI GP

**M12**

◆ TRITON SCA ST+

Montalescot G Lancet 2009 ; 373 : 723-31

Clopidogrel : **300** / 75 mg .....600 = 40%

Ticagrelor : 180 / 90x2 mg

◆ 9 ANS D'ATTENTE

| Critère           | Ticagrelor  | Clopidogrel | p      |
|-------------------|-------------|-------------|--------|
|                   | 2463        | 2486        |        |
| <b>DCV/IM/AVC</b> | <b>7,9%</b> | <b>8,6%</b> | -      |
| DCV               | 3,7%        | 4,0%        | -      |
| IM                | 3,9%        | 5,0%        | 0,064  |
| AVC               | 1,1%        | 0,6%        | -      |
| Thr.Stent         | 2,8%        | 4,2%        | 0,0082 |
| Décès             | 4,2%        | 4,7%        | -      |
| Hémorragies       | 6,7%        | 6,8%        | -      |

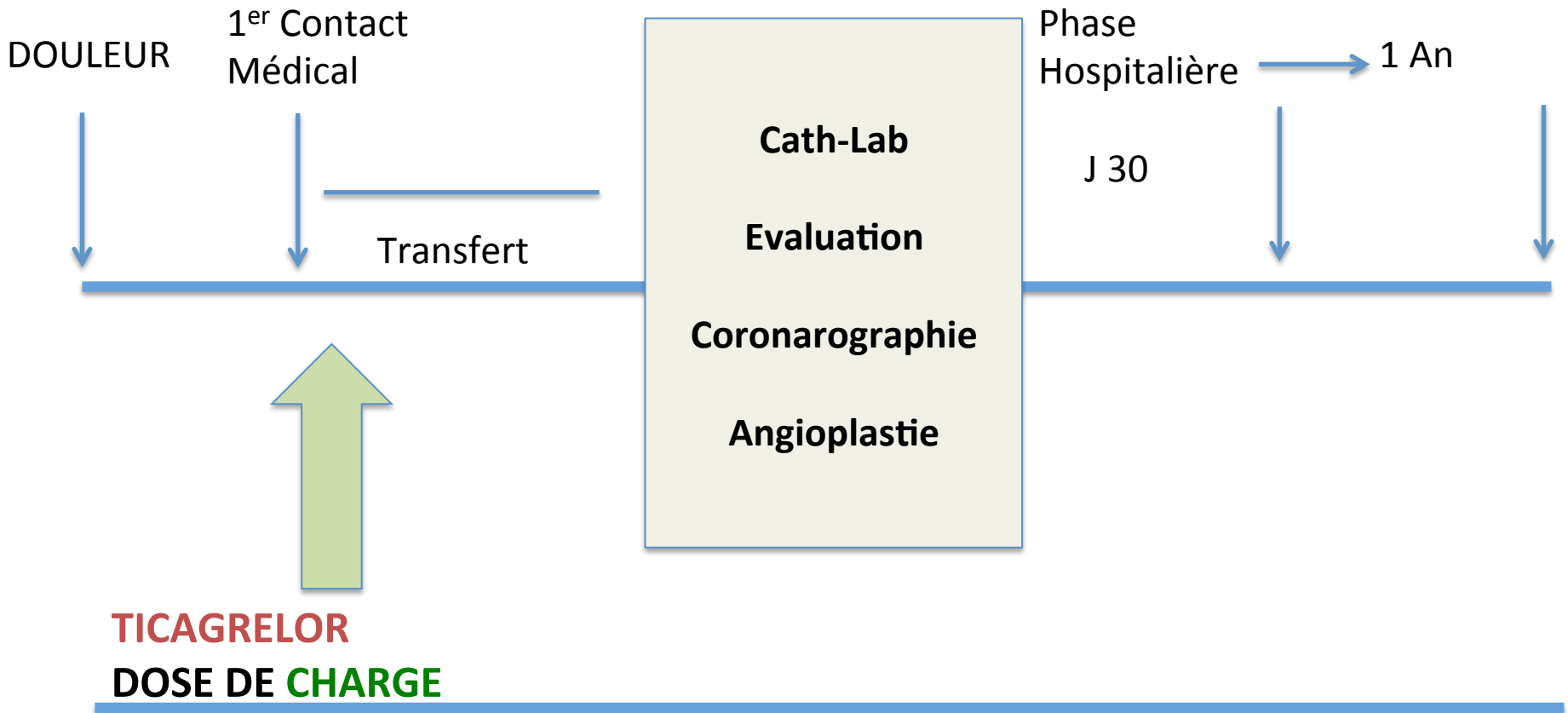
SCA ST+  
ACT primaire :  
66%

50%  
ANTI GP

◆ PLATO SCA ST+

DYSPNEES PAROXYSTIQUES – BRADYCARDIES : 20%

# TICAGRELOR PREHOSPITALIER vs HOSPITALIER



ATLANTIC et ATLANTIC H24

Montalescot G

NEJM 2014 – JACC 2016

# TICAGRELOR PREHOSPITALIER vs HOSPITALIER

Gain : 31 mn

| Ticagrelor     | Prehospital | Hospital | p    |
|----------------|-------------|----------|------|
| TIMI 3 initial | 17%         | 17%      | -    |
| TIMI 3 final   | 82%         | 82%      | -    |
| ST resolution* | 75%         | 72%      | 0,05 |
| Décès H 24     | 1,1%        | 0,2%     | 0,05 |

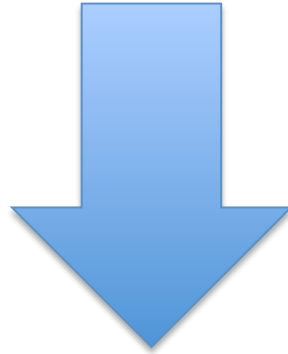
ATLANTIC et ATLANTIC H24

Montalescot G

NEJM 2014 – JACC 2016

◆ PLUS PUISSANTS

◆ PLUS CONSTANTS



**ABSENCE DE BENEFICE CLINIQUEMENT PERTINENT**

**L'ENIGME ?**

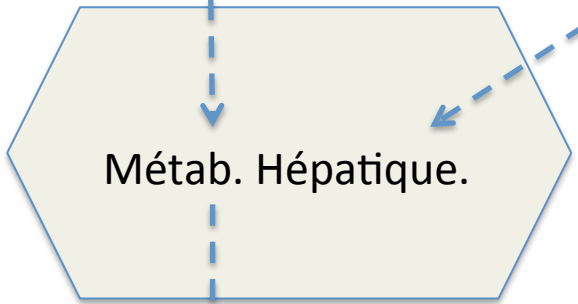
◆ SCA ST+

◆ Clopidogrel-Prasugrel

◆ Ticagrelor

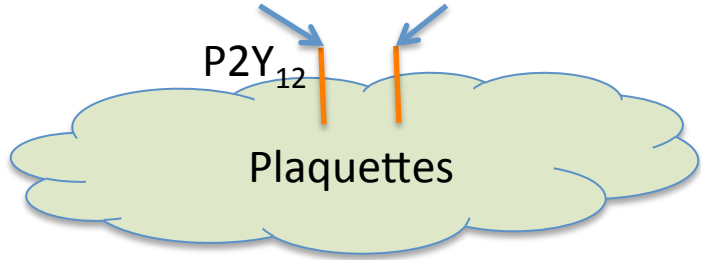


- Nausées
- Vomissements
- Hémodynamique
- Hyperadrénergie
- Morphine**
- PPI's**
- Transporteur
- P-Glycoprotéine

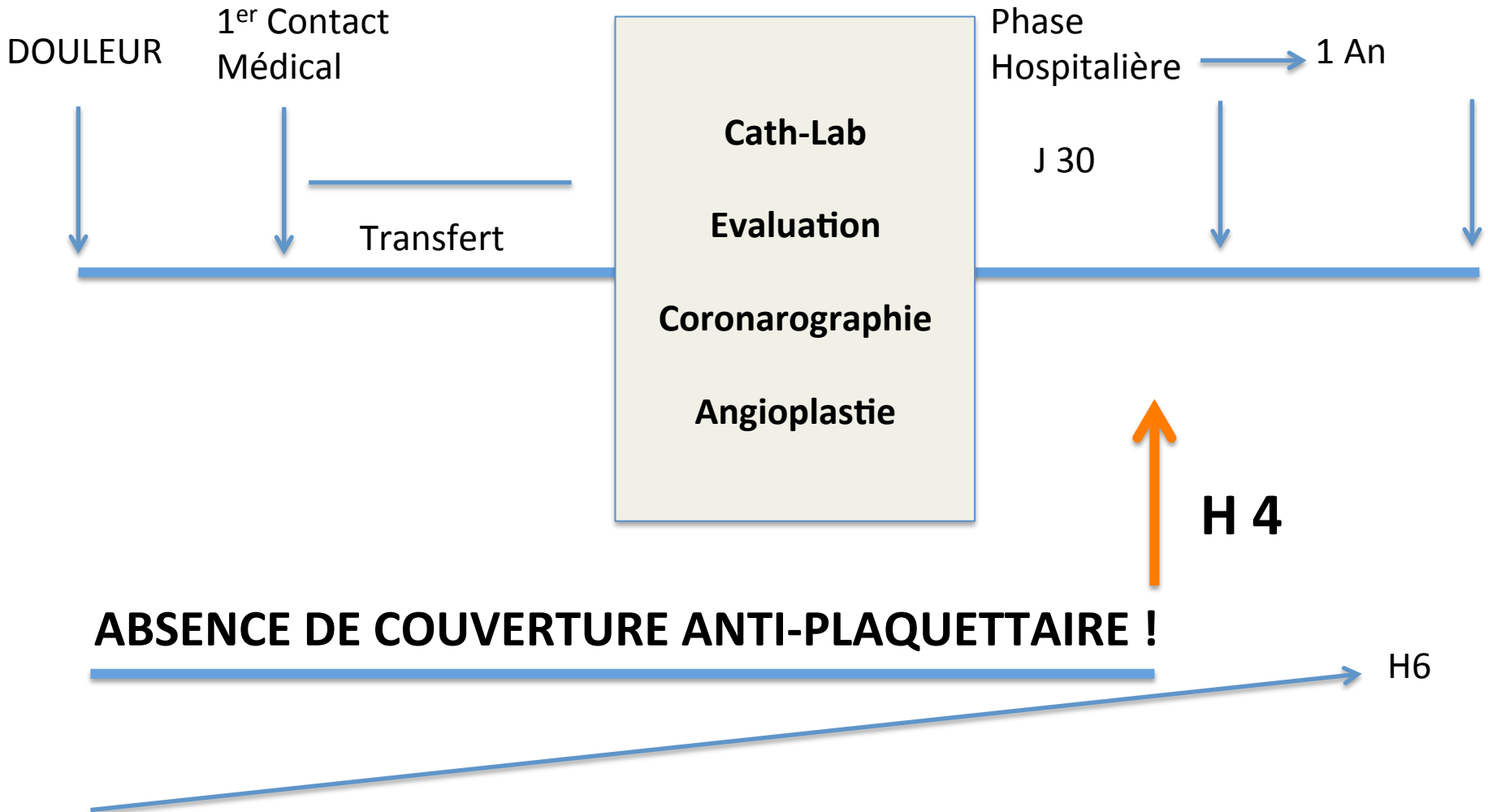


80%

◆ Molécules Actives



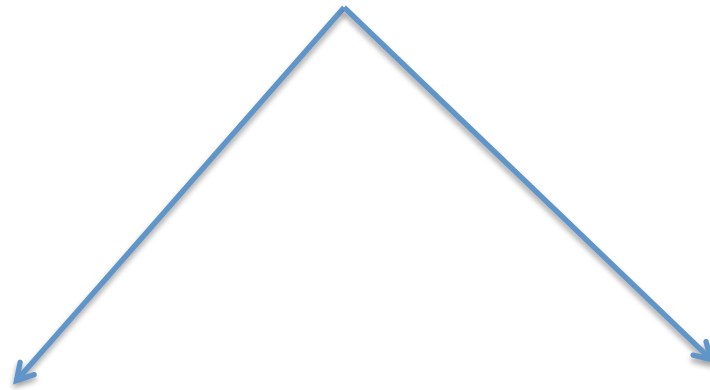
ça ne peut pas marcher !





# ◆ ISAR-REACT 5

PRASUGREL vs TICAGRELOR



◆ SCA ST+

◆ SCA ST-



**CRITERES DE JUGEMENT IDENTIQUES !**

# ◆ CONCLUSION

- ◆ CLOPIDOGREL : 600 mg puis 75 mg
- ◆ BOLUS D'ANTI GP IV puis in situ (charge thrombotique)
- ◆ IV antiP2Y<sub>12</sub> ?
- ◆ CLOPIDOGREL : 75 mg
- ◆ VASP test ?
- ◆ DES dernière génération
- ◆ Surcoût = 100 M Euros/An / SCA ST+ (Brilique)

**The show must go on !**



## Arrêt Précoce

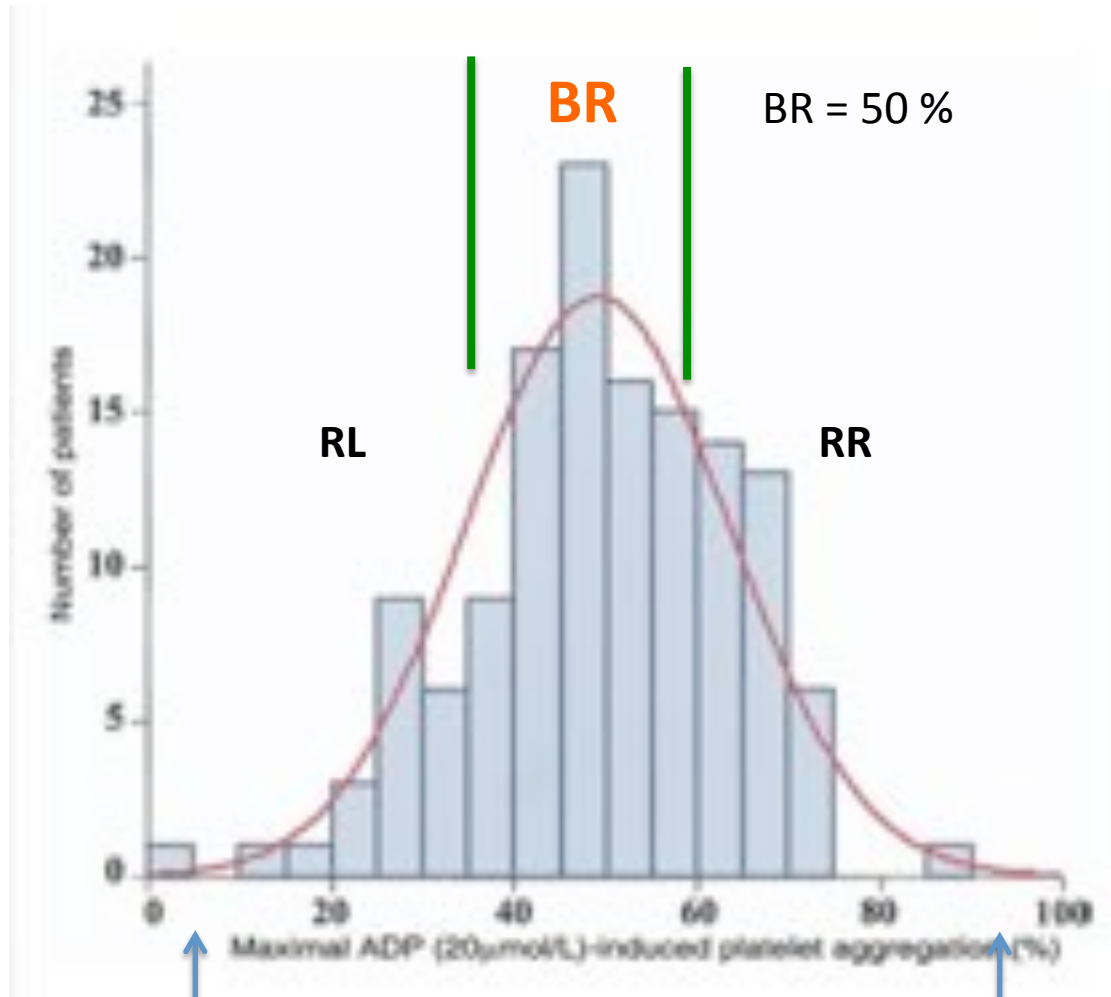
|          | Prasu + Biva | Clopi + Hep | p |
|----------|--------------|-------------|---|
|          | 242          | 254         |   |
| CEP      | 15,6%        | 14,5%       | - |
| ISCHEMIA | 5,5%         | 4,8%        | - |
| BLEEDING | 14,1%        | 12,0%       | - |

◆ BRAVE-4

Schulz S

Eur Heart J 2014 ; 35 : 2285-94

# ◆ VARIABILITE DE LA REPONSE BIOLOGIQUE DU CLOPIDOGREL



Angiolillo DJ  
JACC 2007

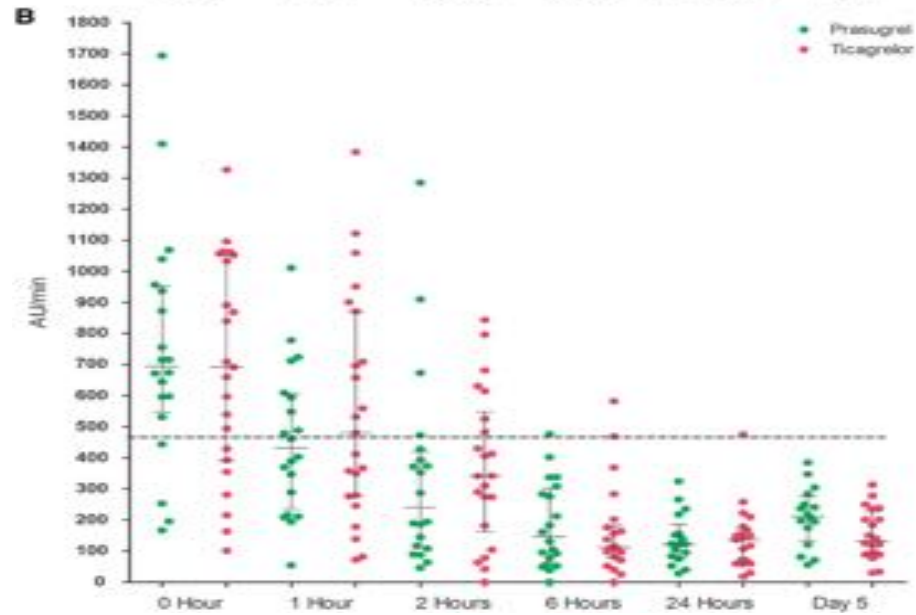
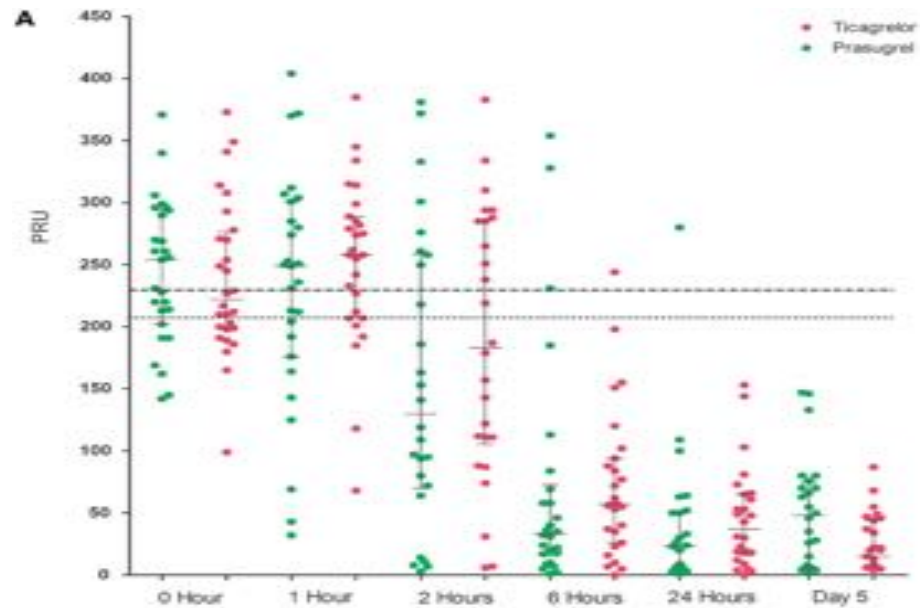
**NR**  
**RETHROMBOSE**

**HR**  
**R.HEMORRAGIQUE**

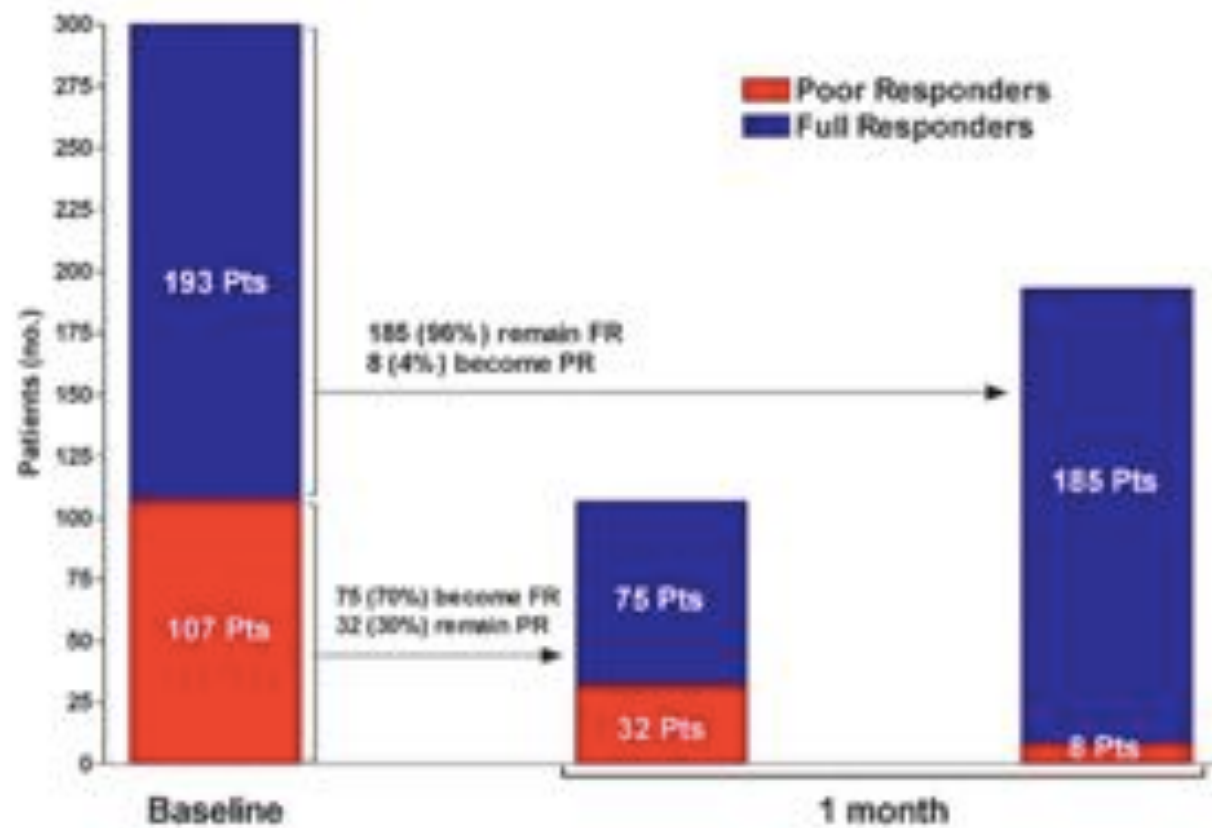
# ◆ DELAI ET VARIABILITE

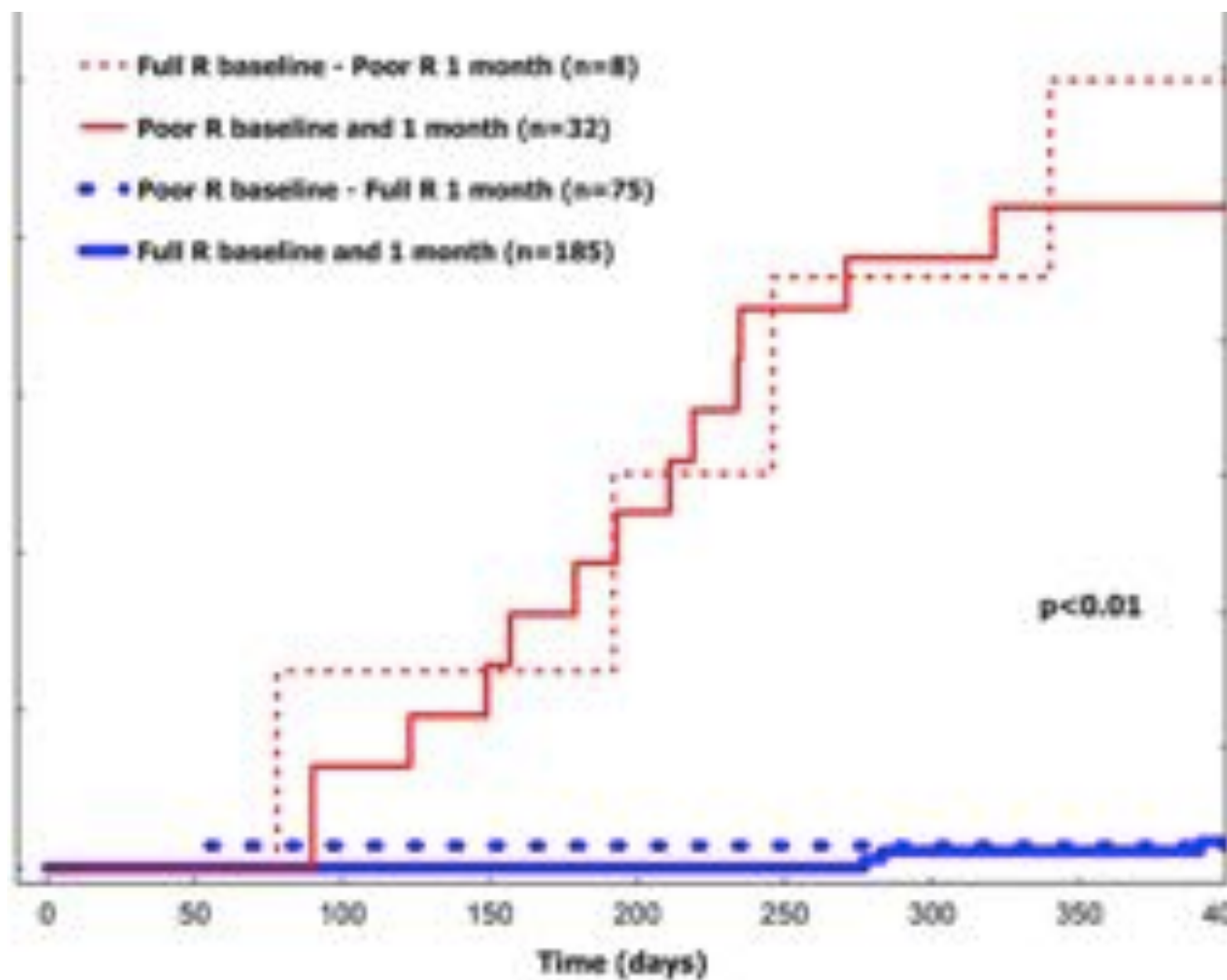
| % Inhibition | Ticagrelor | Ecart         | Prasugrel | Ecart         |
|--------------|------------|---------------|-----------|---------------|
| H1           | 0          | 0             | 0         | 0 - 5         |
| H2           | <b>12</b>  | <b>0 - 54</b> | <b>48</b> | <b>0 - 72</b> |
| H6           | 76         | 61 - 89       | 85        | 65 - 94       |

Alexopoulos D Circ Cardiovasc Interv 2012 ; 5 : 797-804











# TICAGRELOR PREHOSPITALIER vs HOSPITALIER

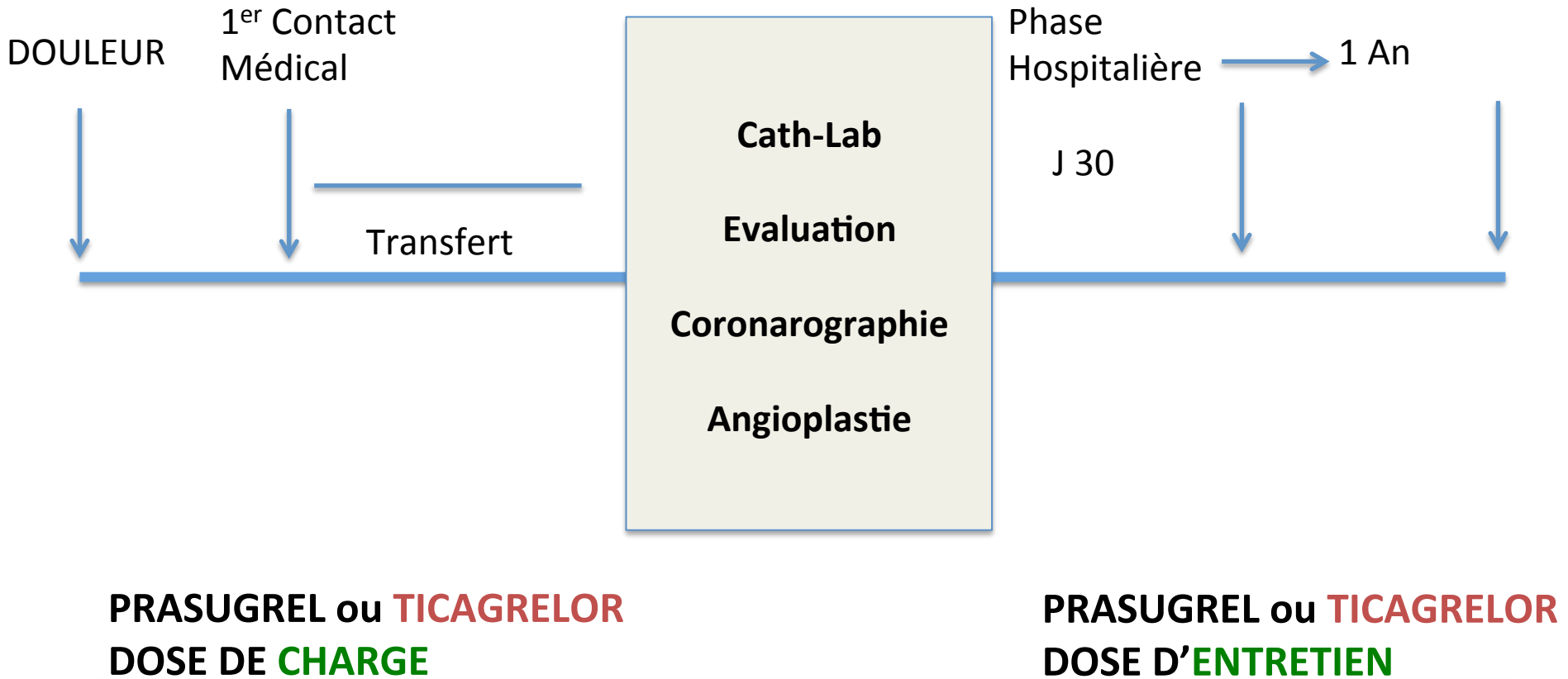
| Ticagrelor     | Prehospital | Hospital | p    |
|----------------|-------------|----------|------|
| TIMI 3 initial | 17%         | 17%      | -    |
| TIMI 3 final   | 82%         | 82%      | -    |
| ST resolution* | 75%         | 72%      | 0,05 |
| Décès H 24     | 1,1%        | 0,2%     | 0,05 |

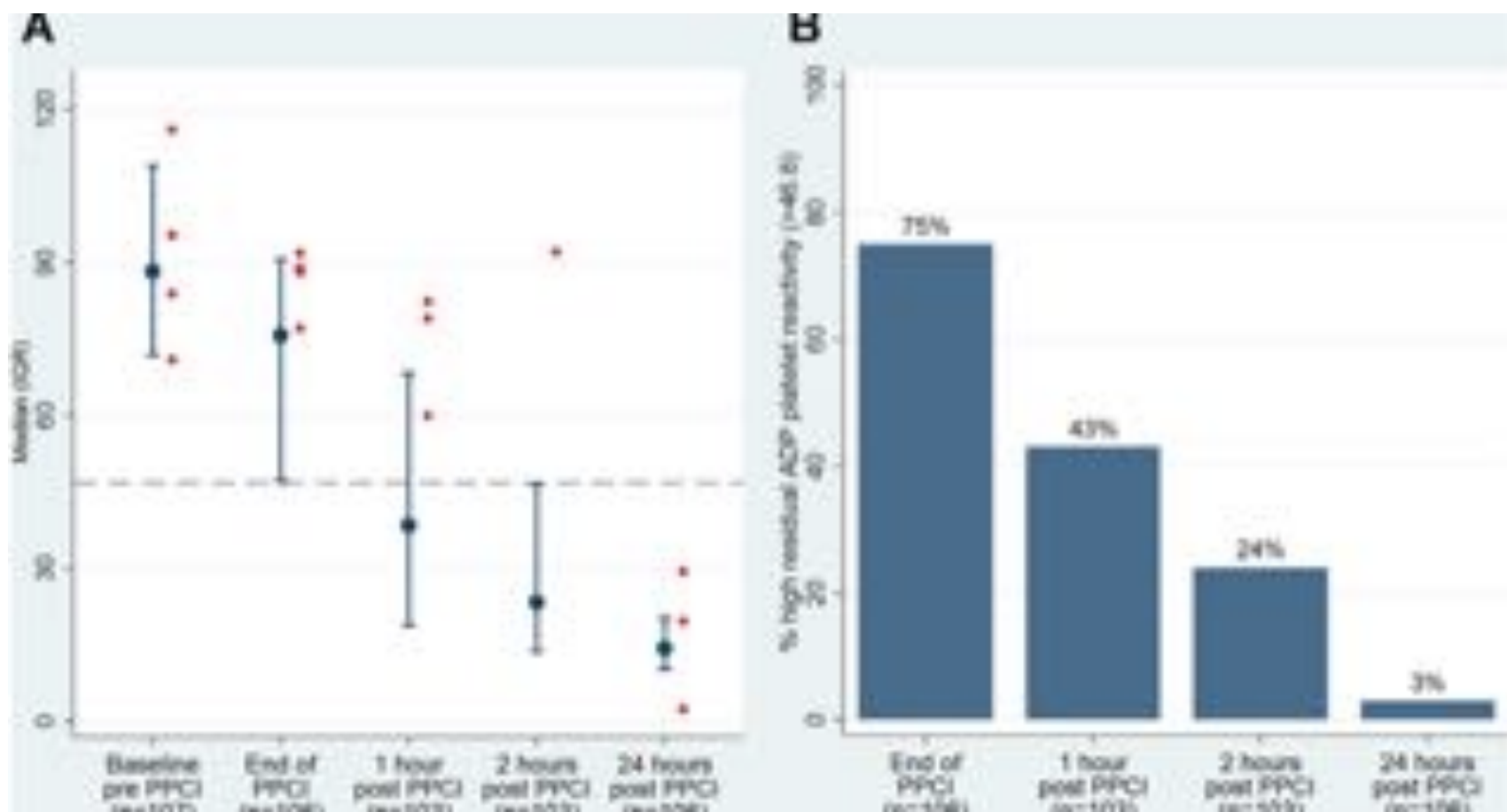
ATLANTIC et ATLANTIC H24

Montalescot G

NEJM 2014 – JACC 2016

# TOUT EN UN !





# LIMITES DU CLOPIDOGREL

## ◆ VARIABILITE REPONSE BIOLOGIQUE

◆ NON-REPONDEURS

◆ METABOLISME HEPATIQUE COMPLEXE (CYT P450)

◆ POLYMORPHISMES GENETIQUES (CYP2C19 ,CYP3A/4.....)

◆ INTERACTIONS MEDICAMENTEUSES (IPP - Inh.Calciques ....)

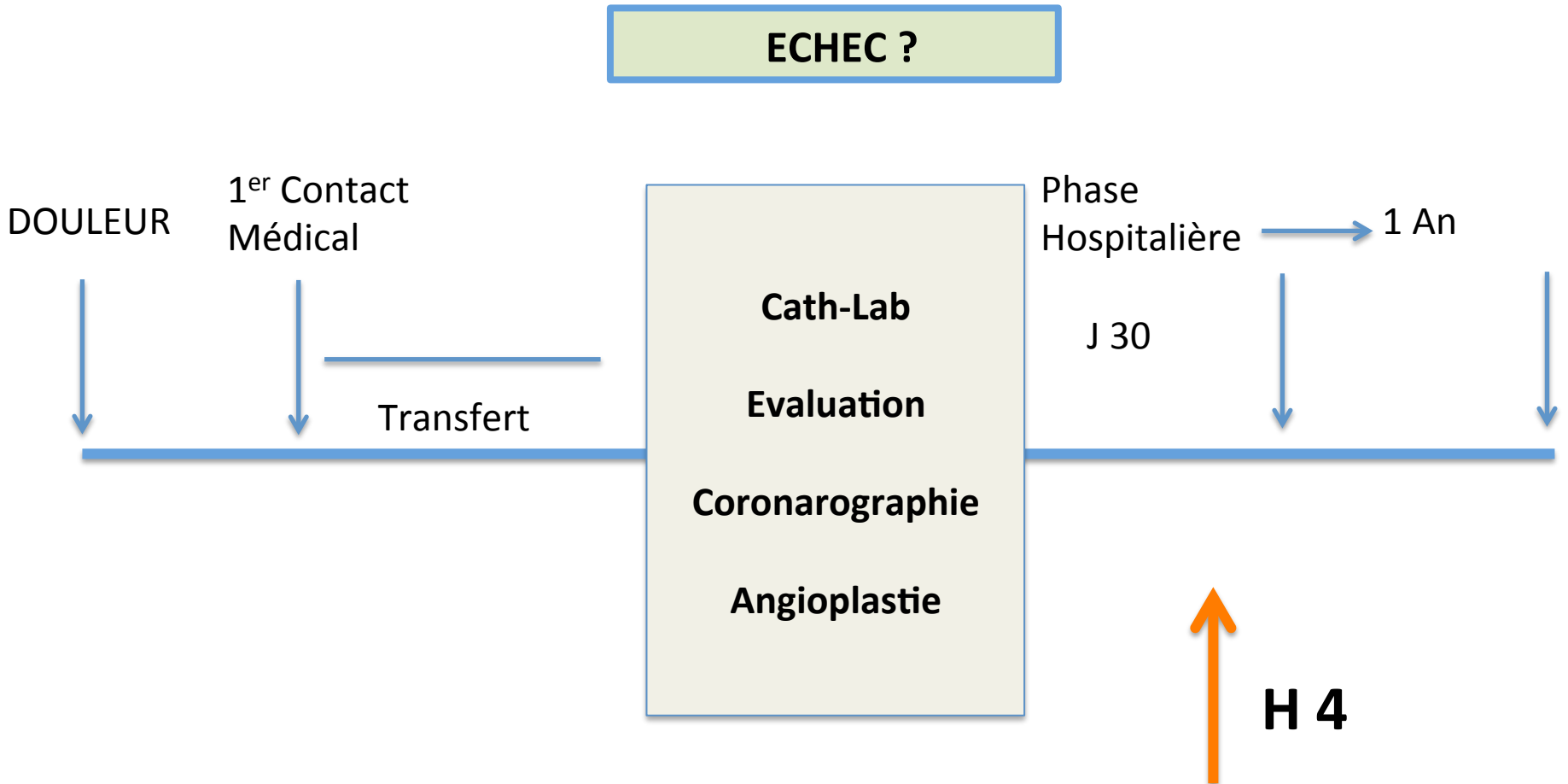


**15 % Molécule Active**

**ESSAIS NON DEDIES AU SCA ST+**

**AUTRE MALADIE**





**ABSENCE DE COUVERTURE ANTI-PLAQUETTAIRE !**

**BOLUS D'ANTI GPIIb/IIIa ? / AP Injectables ?**

# No-Reflow et Embolies Distales



# LE BALLON CLEARWAY

## L' Outil Attendu Pour l' Infarctus du Myocarde ?



JP Monassier , J Shayne

Fondation du Diaconat

Mulhouse

| Platelet Function Testing | Definition                            | Clinical Impact                                   |
|---------------------------|---------------------------------------|---|
| PA                        | Platelet Aggregation (units)          | Measured at Any Time (including before treatment) |
| PI                        | Platelet Inhibition (%)               | Biologic Effect of Treatment                      |
| HPR                       | High Platelet Reactivity              | Bleeding Risk                                     |
| LPR                       | Low Platelet Reactivity               | Ischemic Risk                                     |
| HTPR                      | High on Treatment Platelet Reactivity | Ischemic Risk                                     |
| LTPR                      | Low on Treatment Platelet Reactivity  | Bleeding Risk                                     |
| NR                        | Non Responders                        | <b>PI &lt; 10 %</b>                               |
| GR                        | Good Responders                       | <b>PI : 30 - 50 %</b>                             |
| HR                        | Enhanced Responders                   | <b>PI : &gt; 85 %</b>                             |
| Therapeutic Window        | Low Bleeding = Low Ischemic Events    | Values Depending on the assay                     |

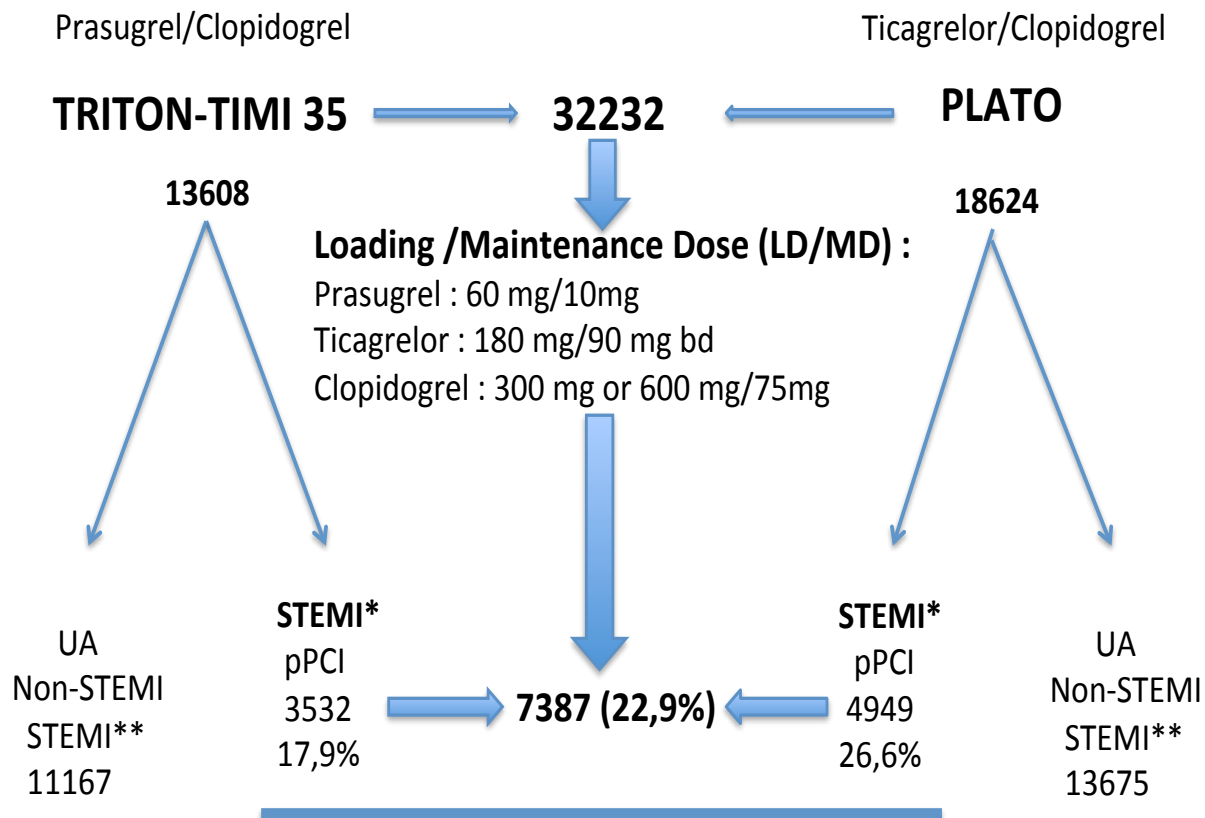


Figure 1 : Populations in TRITON and PLATO

\*STEMI treated in Emergency (pPCI)

**TOUS SCA !**

| Event       | Q 1 : < 95 | Q2 : 95-159 | Q3:160-215 | Q4:216-275 | Q5:>275 | p     |
|-------------|------------|-------------|------------|------------|---------|-------|
|             | 1690       | 1669        | 1691       | 1706       | 1692    |       |
| Deaths      | 2,9%       | 2,9%        | 3,9%       | 4,3%       | 5,0%    | 0,006 |
| MI*         | 4,3%       | 3,7%        | 4,3%       | 4,9%       | 6,5%    | 0,001 |
| ST**        | 0,7%       | 0,8%        | 1,0%       | 1,3%       | 1,8%    | 0,025 |
| Bleeding*** | 11,2%      | 8,3%        | 8,1%       | 8,0%       | 9,1%    | 0,006 |

**Table : Relationship between PRU and Severe Clinical Events – From ADAPT-DES ( )**

| <b>LD</b>       | <b>300 mg</b> | <b>600 mg</b> |
|-----------------|---------------|---------------|
| Non Responders  | 25,9%         | 17,4%         |
| Semi-Responders | 25,9%         | 8,6%          |
| Responders      | 48,1%         | 73,9%         |

Table 9 : Biological comparison between Clopidogrel 300 with 600 mg LD at H4 (Angiolillo)

|             | LTPR        | GR (PRU:178-239)*<br>Therapeutic Window | HTPR        | p      |
|-------------|-------------|---|-------------|--------|
| % / 30 days | 33          | 33                                      | 33          |        |
| NACE %*     | <b>14,1</b> | <b>7,8</b>                              | <b>15,4</b> | 0,025  |
| Ischemia %  | 4,0         | 4,9                                     | <b>15,0</b> | 0,0001 |
| Bleeding %  | <b>10,5</b> | 2,9                                     | 1,3         | 0,0001 |

Table 10 : ARMYDA PROVE : Events rate depending on Platelet Reactivity level \*NACE : Net Clinical Adverse Events .



|               |                 |             |                            |
|---------------|-----------------|-------------|----------------------------|
| <b>TRITON</b> | Prasugrel       | Clopidogrel | Aspirin                    |
| LD            | 60 mg           | 300 mg      | 325 mg orally<br>500 mg IV |
| MD            | 10 mg           | 75 mg       | 75 - 162 mg                |
| <b>PLATO</b>  | Ticagrelor      | Clopidogrel | Aspirin                    |
| LD            | 180 mg          | 300 mg*     | 325 mg                     |
| MD            | 90 mg twice/day | 75 mg       | 75-100 mg**                |

Table 2 : Loading and Maintenance Doses :  
AntiP2Y<sub>12</sub>s and Aspirin .

40% : 600 mg      \*\* 325 mg allowed for 6  
months .

| STEMI<br>pPCI M12 -<br>Definite ST | Clopidogrel<br>N=2486 | Ticagrelor<br>N=2463 | p     | ARR / AIR | NNT / NNH |
|------------------------------------|-----------------------|----------------------|-------|-----------|-----------|
| Early<br>(<24hrs)                  | 0,2 %                 | 0,5 %                | ?     | - 0,3 %   | - 333     |
| Up to 30 days                      | 1,6 %                 | 1,0 %                | ?     | 0,6 %     | 167       |
| 30 d. to One<br>Year               | 0,7 %                 | 0,4 %                | ?     | 0,3 %     | 333       |
| All Definite<br>ST                 | 2,3 %                 | 1,4 %                | 0,01  | 0,9 %     | 111       |
| All. Definite<br>or Probable<br>ST | 3,4 %                 | 2,3 %                | 0,01  | 1,1%      | 91        |
| All Any ST                         | 4,2 %                 | 2,8 %                | 0,008 | 1,4 %     | 71        |

Table 4 : Stent Thrombosis in PLATO (pPCI)  
\*Definite ST

| <b>Initial Flow</b> | <b>TIMI 0-2</b> | <b>TIMI 3</b> | <b>p</b> | <b>ARR*</b> | <b>NNT**</b> |
|---------------------|-----------------|---------------|----------|-------------|--------------|
| Final TIMI-3 Flow   | 91,4%           | 98,1%         | 0,0001   | 6,7%        | 15           |
| In-hospital Deaths  | 2,4%            | 0,5%          | 0,02     | 1,9%        | 53           |
| Cardiac Failure     | 11,2%           | 6,7%          | 0,002    | 4,5%        | 22           |
| 6 m. deaths***      | 4,4%            | 0,5%          | 0,009    | 3,9%        | 26           |

Table I : prePCI flow and outcome in STEMI .  
 \*Absolute Risk Reduction \*\*Number Needed to Treat \*\*\* all causes deaths (from 30)

| <b>Bleeding Predictors</b>       |   |
|----------------------------------|---|
| Femoral access site              | Hypertension                                      |
| Long Procedure                   | Prasugrel   |
| Age > 75                         | Transfusions                                      |
| Female Sex                       | Body Weight < 60 kg                               |
| Hypercholesterolemia             | CKD   |
| Anemia                           | Previous Cerebral Event                           |
| Hyperleukocytosis                | Atrial Fibrillation - Coumadin and Triple Therapy |
| Patient Compliance (information) | "Bruising"  |

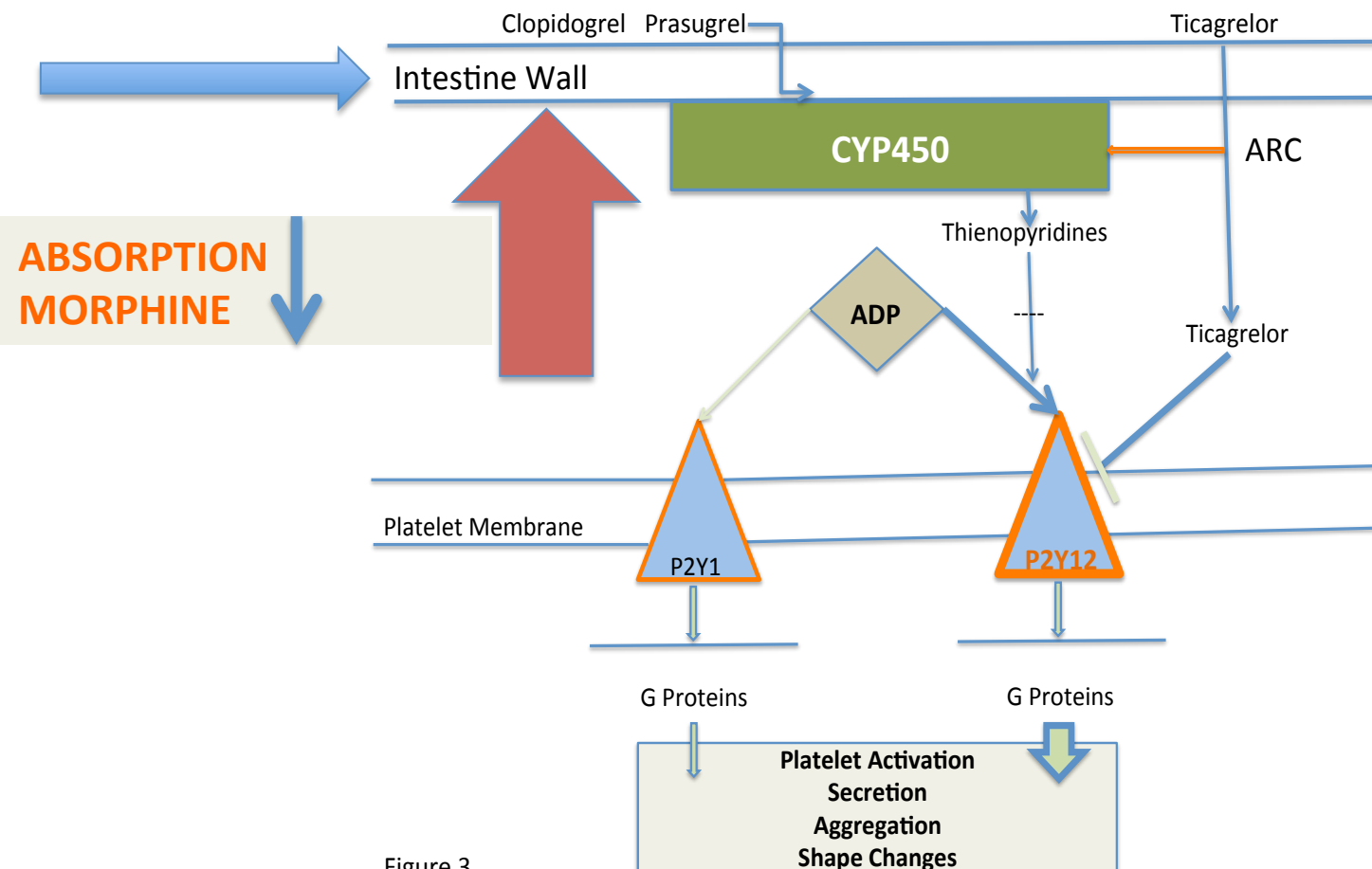


Figure 3

Figure 1 : Thienopyridines block ADP linking to P2Y<sub>12</sub>. Ticagrelor acts directly on the receptor .

**RALENTISSEMENT DU TRANSIT : Vomissements – Nausées – Hémodynamique**  
**DIMINUTION DE L'ABSORPTION : Transporteur P-Glycoprotéine**