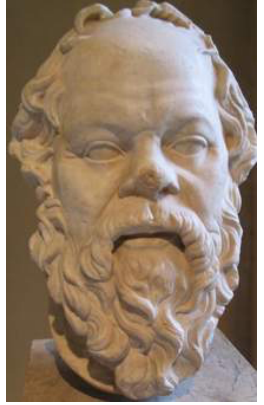
Socrates
Ticagrelor vs Aspirin in Acute Stroke or Transient Ischemic Attack



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ORIGINAL ARTICLE

Ticagrelor versus Aspirin in Acute Stroke or Transient Ischemic Attack

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Conflits d'intérêts potentiels

- Comité Aviseur
  - Bayer
  - BMS Pfizer

- RECHERCHE
  - NIH
  - Astra Zeneca *
  - Bayer
  - BI

Ticagrelor

- Antiplaquettaire
  - antagoniste réversible des récepteurs plaquettaires P2Y12
- Début d'action RAPIDE
- Moins de variabilité individuelle dans l'activité antiplaquettaire
- Utilisé dans le management du SCA: (PLATO *2009* Ticagrelor vs Clopidogrel)
  - Ticagrelor 90 mg bid plus ASA code CV161
- Utilisé dans d'autres études du programme PARTHENON de Astra Zeneca
  - PEGASUS-TIMI 54
  - EUCLID, THEMIS

SOCRATES introduction

- Risque de récurrence d'AVC : 10-15% dans les premier 90 jours
- 22% risque long terme sous ASA
- ASA: risque d'hémorrhagie RR rate 1.5-3.1 incluant GI

Design de SOCRATES: multi centrique, double insu, de jan **2014** à oct **2015**, 672 sites , 33 pays

- AVC aigu NIH 5 ou moins
  ou
- ICT haut risque ABCD : 4+

Moins de 24h

- Pas de TPA
- Pas de FA
- Pas d'HX d'HIC
- Pas de revascularisation carotidienne planifiée court terme ;carotide symptomatique

Ticagrelor 180mg dose de charge jour 1
Ticagrelor 90 mg BID jour 2 à 90

ASA 300 mg dose de charge jour 1
ASA 100 md die jour 2 à 90

Suivi 90 jours

Endpoint primaire

120 jours: Safety analysis

SOCRATES Objectifs/et « End Points »

- Primaire
  - AVC (ischémic ou hémorrhagique), IM et Décès
- Secondaire *(hiearchical)*
  - AVC ischémique seul
  - 5 Autres
- « Safety »:
  - Événement hémorrhagique majeur selon la définition de PLATO
    - (Fatal, HIC, chute Hb ou transfusions)

SOCRATES: Baseline age moyen: 66 ans

Table 1. Baseline Characteristics of the Participants.*

Characteristic	Ticagrelor (N=6589)	Aspirin (N=6610)
Age — yr	65.8±11.23	65.9±11.37
Female sex — no. (%)	2759 (41.9)	2724 (41.2)
Race — no. (%)†		
White	4374 (66.4)	4410 (66.7)
Black	119 (1.8)	120 (1.8)
Asian	1957 (29.7)	1949 (29.5)
Other	139 (2.1)	131 (2.0)
Ethnic background — no. (%)†		
Not Hispanic	6023 (91.4)	6050 (91.5)
Hispanic	566 (8.6)	558 (8.4)
Region — no. (%)		
Asia or Australia	1990 (30.2)	1981 (30.0)
Europe	3769 (57.2)	3772 (57.1)
North America	514 (7.8)	540 (8.2)
Central or South America	316 (4.8)	317 (4.8)
Median blood pressure (interquartile range) — mm Hg		
Systolic	150 (137.0–165.0)	150 (135.5–165.0)
Diastolic	84 (78.0–92.0)	84 (77.0–91.0)
Median body-mass index (interquartile range)‡	26.1 (23.5–29.4)	26.0 (23.5–29.3)
Medical history — no. (%)		
Hypertension	4797 (72.8)	4933 (74.6)
Dyslipidemia	2531 (38.4)	2497 (37.8)
Diabetes mellitus	1664 (25.3)	1548 (23.4)
Previous ischemic stroke	765 (11.6)	828 (12.5)
Previous TIA	410 (6.2)	446 (6.7)
Previous myocardial infarction	280 (4.2)	268 (4.1)
Coronary artery disease	573 (8.7)	571 (8.6)
Congestive heart failure	234 (3.6)	248 (3.8)
Taking aspirin before randomization — no. (%)	2130 (32.3)	2102 (31.8)
Taking clopidogrel before randomization — no. (%)	219 (3.3)	237 (3.6)
Time to randomization after onset of symptoms — no. (%)		
<12 hr	2400 (36.4)	2424 (36.7)
≥12 hr	4188 (63.6)	4186 (63.3)
Qualifying event — no. (%)		
TIA	1790 (27.2)	1741 (26.3)
Ischemic stroke	4798 (72.8)	4869 (73.7)
Baseline $ABCD^2$ score among patients with TIA as qualifying event — no./total no. (%)§		
≤5	1313/1790 (73.4)	1257/1741 (72.2)
>5	471/1790 (26.3)	479/1741 (27.5)
Baseline NIHSS score among patients with ischemic stroke as qualifying event — no./total no. (%)¶		
≤3	3235/4798 (67.4)	3282/4869 (67.4)
>3	1541/4798 (32.1)	1566/4869 (32.2)

* The differences in baseline characteristics between the treatment groups were not significant, with the exception of the proportions of patients with a history of diabetes or hypertension (nominal P<0.05). TIA denotes transient ischemic attack.
† Race and ethnic background were self-reported.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ $ABCD^2$ stroke risk scores range from 0 to 7, with higher scores indicating higher risk; data are provided only for the group of 3531 patients for whom TIA was the qualifying event for inclusion in the trial.
¶ National Institutes of Health Stroke Scale (NIHSS) scores range from 0 to 42, with higher scores indicating more severe stroke; data are provided only for the group of 9667 patients for whom ischemic stroke was the qualifying event for inclusion in the trial.

13,199 patients

Peu de perte au suivi: Moins que 2

Pas de différence,

Sauf

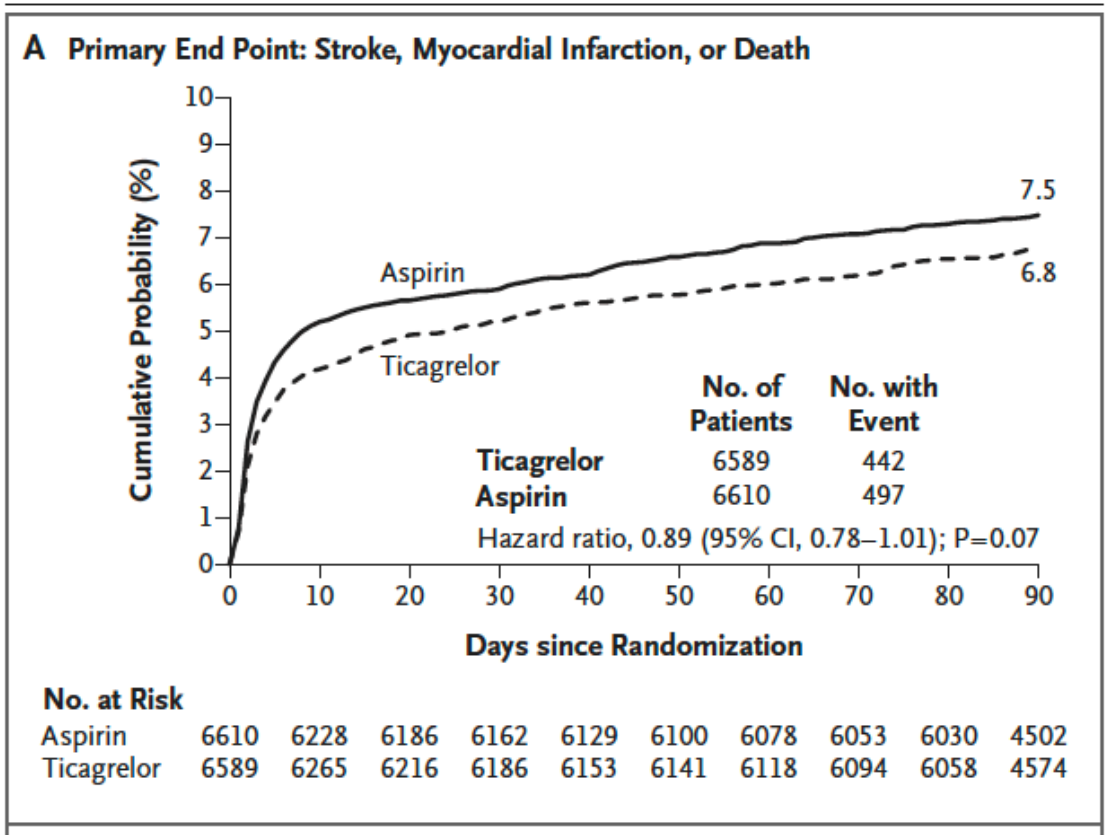
- Un peu plus de diabétiques dans le groupe Ticagrelor
- Un peu plus d'hypertendus dans le groupe ASA

16% ont cessé la médication de l'étude prématurément

17.5% Ticagrelor

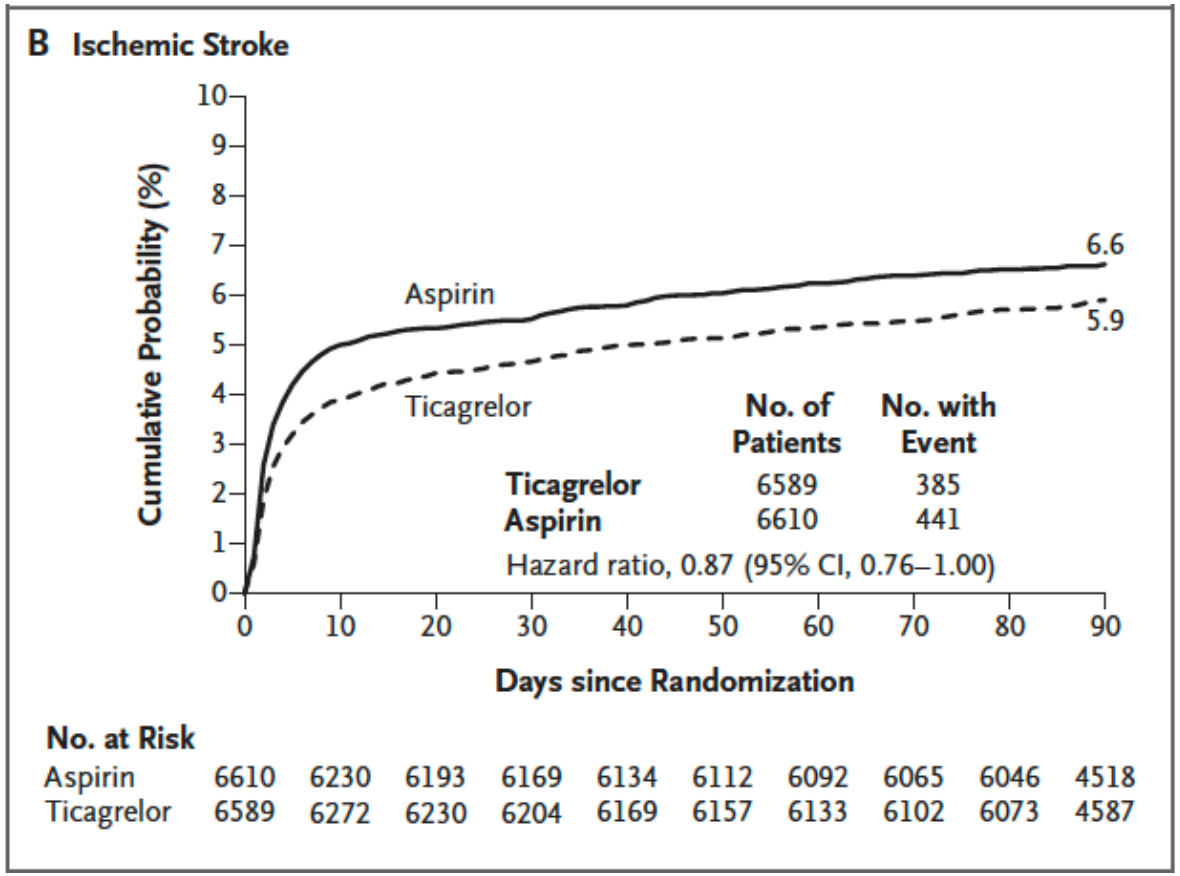
14.7% ASA

SOCRATES: Résultats AVC, IM , DÉCES



- AVC, IM, Décès à 90 jours
- Ticagrelor : 6.8%
- ASA: 7.5%
- HR: 0.89 (0.78-1.01)
- P=0.067 NS

SOCRATES: Résultat AVC ischémique 90 jours



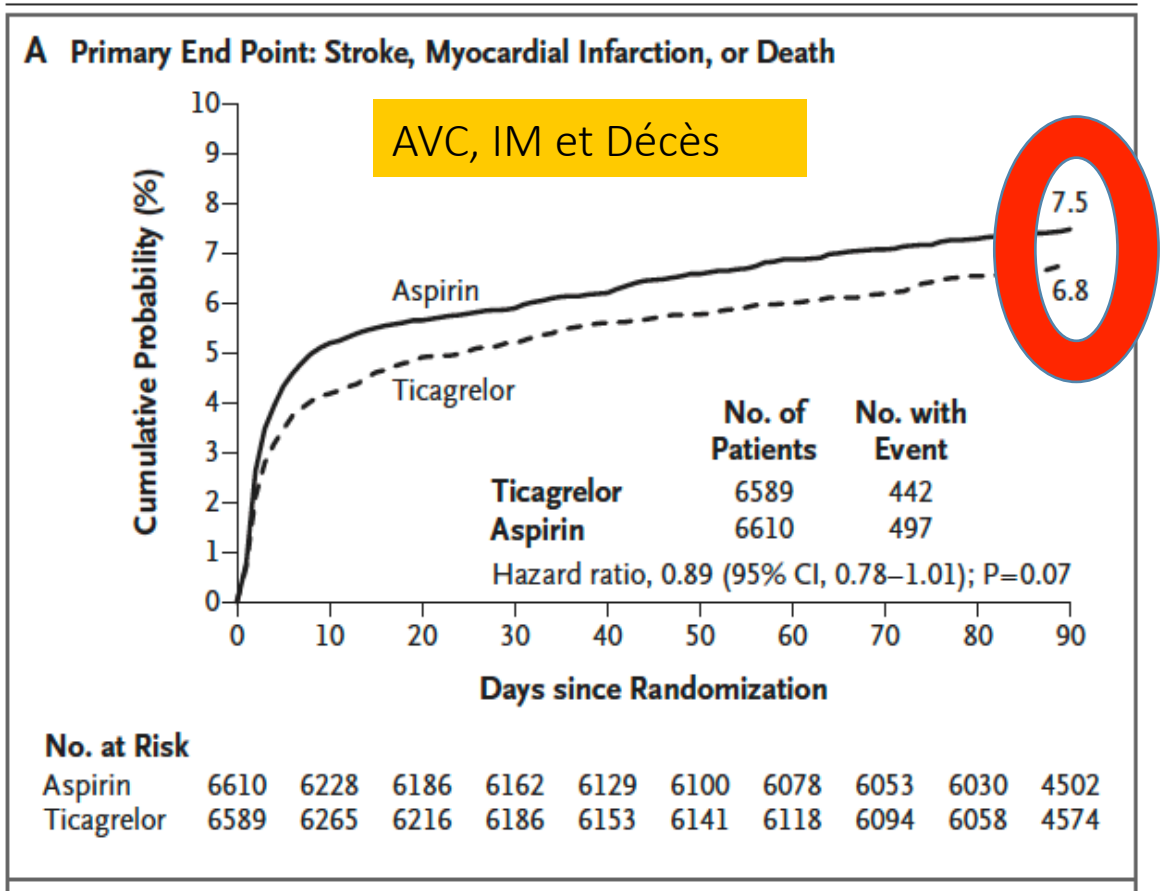
- AVC à 90 jours
- Ticagrelor : 5.9%
- ASA: 6.6%
- HR: 0.87 (0.76-1.00)
- P=0.046 nominal
- *Considéré NS en accord avec l'analyse hierarchique*

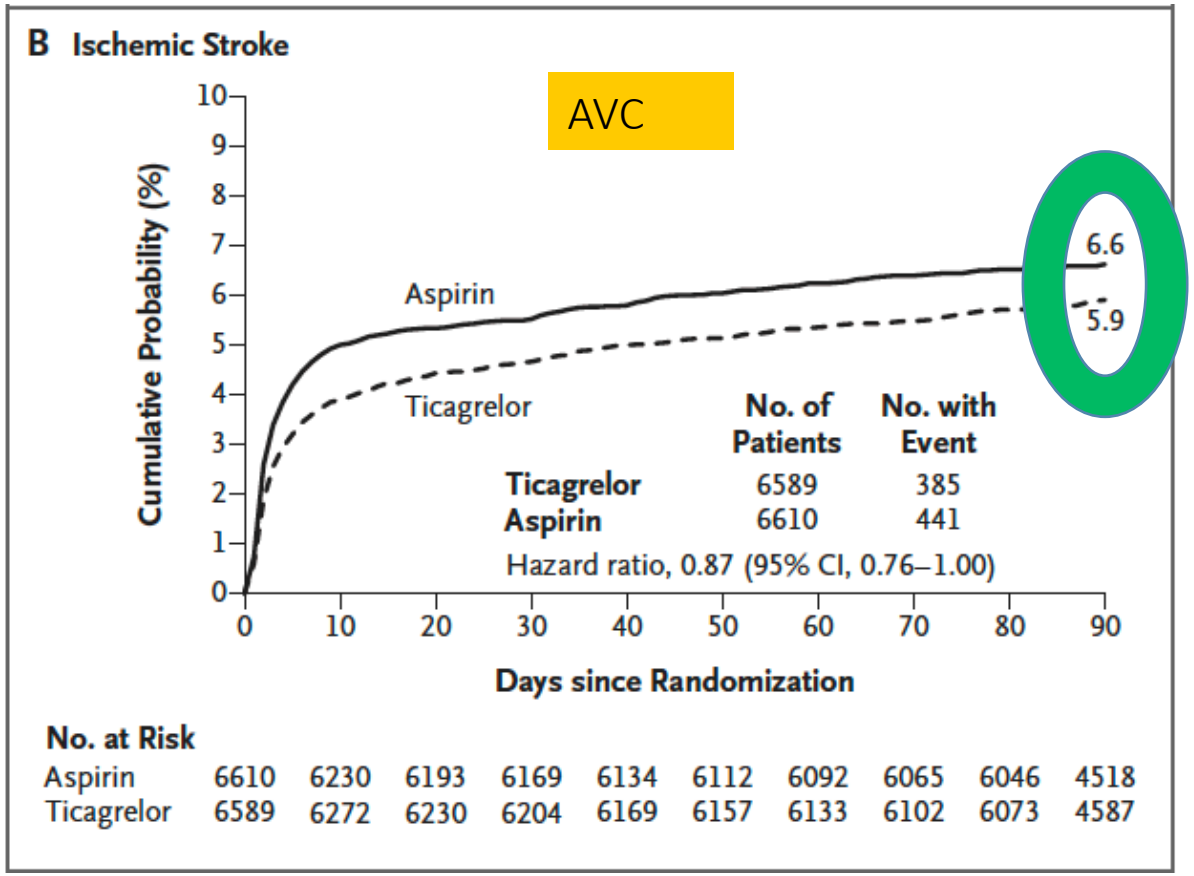
Moins que le 10-15% cité dans intro

<u>Exclusions de</u>
-cas sévères
-Sténose carot. symp.
-TPA
-pts sous ASA ?

† Ischemic stroke was the only secondary end-point event to be tested in a hierarchical testing sequence if there was a significant difference between the treatment groups with regard to the primary end point; analyses of all other secondary end points were prespecified but considered to be exploratory.
‡ The P value was considered nonsignificant in accordance with the hierarchical testing plan.

SOCRATES : Résultats





La première semaine

SOCRATES: Résultat primaire AVC, IM, Décès

- AVC, IM, Décès à 90 jours

- Ticagrelor : 7.5%
- ASA: 6.8%
- HR: 0.89 (0.78-1.01)
- P=0.067

- AVC, IM, Décès à 7 jours

- Ticagrelor : -----%
- ASA ---------%
- HR: 0.81 (0.68-.95)
- P=0.01 NOMINAL

La première semaine; pas dans l'article

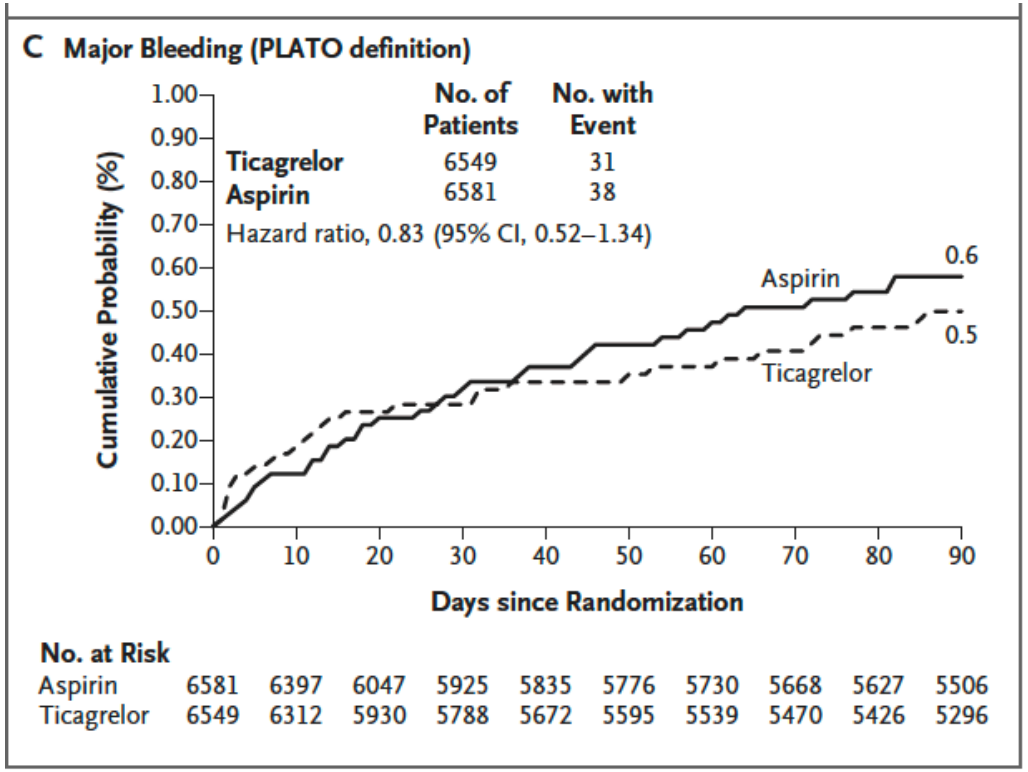
SOCRATES: Résultats des sous groupes

- Tendance vers un bénifice accru avec TICAGRELOR
  - Plus jeunes
  - ICT ou AVC mineur NIH 2 ou moins
  - Traités à l'ASA au préalable: environ 1/3
    - *Double APT en phase aiguë*

MD traitant souvent réticent à randomiser si événement sous ASA car pouvait rester sous ASA seul

Plusieurs voulaient ajouter clopidogrel pour environ 3 semaines

SOCRATES: PROBABILITÉ D'HEMORRHAGIE MAJEURE



Safety end points¶						
Major bleeding	31 (0.5)	0.5	38 (0.6)	0.6	0.83 (0.52–1.34)	0.45
Major bleeding, fatal or life-threatening	22 (0.3)	0.4	27 (0.4)	0.4	0.83 (0.47–1.46)	0.52
Fatal bleeding	9 (0.1)		4 (0.1)			
Intracranial hemorrhage	12 (0.2)	0.2	18 (0.3)	0.3	0.68 (0.33–1.41)	0.30
Major bleeding, other	9 (0.1)	0.1	11 (0.2)	0.2	0.84 (0.35–2.03)	0.70
Major or minor bleeding	106 (1.6)	1.7	82 (1.2)	1.3	1.32 (0.99–1.76)	0.06

ASA: 0.6% n= 38, (18 HIC)
Ticagrelor: 0.5% n= 31 (12 HIC)
NS

SOCRATES: Effets secondaires

- Dyspnée menant à D/C
  - Ticagrelor: 1.4%
  - ASA: 0.3%

- Saignements menant à D/C
  - Ticagrelor: 1.3%
  - ASA : 0.6%

- Survient en général moins de 8 jours après début de ticagrelor 90mg BIB
- Non associée à dysfonction pulmonaire ou cardiaque

Current Controversies
© Schattauer 2012

Why does ticagrelor induce dyspnea?

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Summary
In studies that compared the reversible $P2Y_{12}$ inhibitor ticagrelor with the irreversible inhibitor clopidogrel, dyspnea was observed more frequently among ticagrelor-treated patients than among clopidogrel-treated patients. Because dyspnea was not associated with acidosis, pulmonary or cardiac dysfunction, alterations in the mechanisms and pathways of the sensation of dyspnea may be involved in its pathogenesis. It has been hypothesised that the sensation of dyspnea in ticagrelor-treated patients is triggered by adenosine, because ticagrelor inhibits its clearance, thereby increasing its concentration in the circulation. However, dipyridamole, a much stronger inhibitor of adenosine clearance than ticagrelor, usually does not cause dyspnea. We hypothesise that inhibition of $P2Y_{12}$ on sensory neurons increases the sensation of dyspnea, particularly when reversible inhibitors are used. We base our hypothesis on the following considerations: 1) cangrelor and elinogrel, which, like ticagrelor, are reversible $P2Y_{12}$ inhibitors, also increase the incidence of dyspnea; 2) it is biologically plausible that inhibition of $P2Y_{12}$ on sensory neurons increases the sensation of dyspnea; 3) inhibition of $P2Y_{12}$ on platelets (which do not have a nucleus) by clopidogrel is permanent, despite the once daily administration and the short plasma half-life of the inhibitor; 4) in contrast, inhibition of $P2Y_{12}$ on neurons by clopidogrel may be temporary and transient, because neurons have a nucleus and can therefore rapidly replace the inhibited receptors with newly synthetised ones; 5) inhibition of $P2Y_{12}$ on neurons by reversible inhibitors is permanent, because the plasma drug concentration is maintained high by repeated dosing, in order to ensure permanent inhibition of platelet $P2Y_{12}$.

Keywords
ADP receptors, arterial thrombosis, nervous system

SOCRATES: Commentaires

- « Near miss »
- Importance de la phase aiguë

- Autres données positives Ticagrelor: PLATO,
  - PEGASUS (PAS AIGU: pts avec ATCD d'IM Ticagrelor vs Clopidogrel sur fond d'ASA)

- EUCLID (dans MAP: neg) , THEMIS

- ETUDE POINT: Bithérapie antiplaquettaire dans la prévention secondaire de l'AVC : ASA +/- Clopidogrel (moins de 12h) n= 4000/4576 patients

Guidelines bithérapie antiplaquettaire

ASA + clopidogrel en prévention secondaire d'AVC

- Securité à 90 jours : level A
- Efficacité 90 jours : level C

ii. Short-term concurrent use of ASA and clopidogrel (up to 90 days) has not shown an increased risk of bleeding (Evidence Level A); however, longer-term use is not recommended for secondary stroke prevention, unless there is an alternate indication (e.g. drug-eluting stent requiring dual antiplatelet therapy), due to an increased risk of bleeding and mortality (Evidence Level A).

iii. The combination of ASA (81 mg) and clopidogrel 75 mg is still of uncertain benefit in the Canadian setting for early prevention of recurrent stroke when used within 90 days, and should not be routinely used in all patients (Evidence Level C). *Although the CHANCE clinical trial has demonstrated the efficacy of 21 days ASA and clopidogrel therapy in a Chinese population, the generalization of these findings to the Canadian population and North*  *andards of care remains*

Shelagh B. Coutts[1] Stroke Best Practices Rec. 2014

- AVC mineur ou ICT en dedans de 24 H pour 21 JOURS : level B

- The combination of aspirin and clopidogrel might be considered for initiation within 24 hours of a minor ischemic stroke or TIA and for continuation for 21 days*(Class IIb; Level of Evidence B*). (New recommendation)

Walter Kernan Stroke 2014