Quels critères de choix pour les antiplaquettaires oraux ?

Le étapes du choix depuis le pré-hospitalier jusqu'à la sortie

François Schiele, Besançon

Conflits d'intérêt potentiels :

- Honoraires de communication et de participation à réunions avec tous les laboratoires impliqués dans les antiplaquettaires disponibles, personnels et au profit d'une association de recherche clinique .
- Honoraires d'étude clinique portant sur les anti-thrombotiques utilisés dans les syndrome coronarien aigus au profit d'une association de recherche clinique

8 molécules antiplaquettaires en cas de SCA

Le clinicien dispose de 8 molécules antiplaquettaires qui agissent sur trois cibles:

1. La voie de la cyclo oxygénase: l'Aspirine ;
2. La voie de l'ADP avec 4 molécules inhibant les récepteur P2Y12 :
   - Ticlopidine,
   - Clopidogrel,
   - Prasugrel,
   - Ticagrelor

3.Les récepteurs GP2b3a:
   - Tirofiban,
   - Eptifibatide,
   - Abciximab.

Table 8 $P2Y_{12}$ inhibitors

	Clopidogrel	Prasugrel	Ticagrelor
Class	Thienopyridine	Thienopyridine	Triazolopyrimidine
Reversibility	Irreversible	Irreversible	Reversible
Activation	Prodrug, limited by metabolization	Prodrug, not limited by metabolization	Active drug
Onset of effect[a]	2–4 h	30 min	30 min
Duration of effect	3–10 days	5–10 days	3–4 days
Withdrawal before major surgery	5 days	7 days	5 days

[a]50% inhibition of platelet aggregation.

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8 molécules antiplaquettaires en cas de SCA

Le clinicien dispose de recommandations : ESC, ACC/AHA
Toutes molécules grade IA ou IB…

P2Y12: oui immédiat puis sur 12 mois

Recommendations	Class[a]	Level[b]
…ications at an initial … of treatment strateg…		
…sible and maintained…		
…mbination with DAP… appropriate for patients with … risk factors … of anticoagulants or steroi…	I	A
Prolonged or permanent withdra… ibitors within 12 months after th… event is discouraged unless clinically indicated.	I	C
Ticagrelor (180-mg loading dose, 90 mg twic… recommended for all patients at moderate-to-high risk of ischaemic events (e.g. elevated troponins) , regar… initial treatment strategy and including those pre-treated with clopidogrel (which should be discontinued when ticag… is commenced).	I	B
Prasugrel (60-mg loading dose, 10-mg daily dose) is recommended for $P2Y_{12}$-inhibitor-naïve patients (especially diabetics) in whom coronary anatomy is known and who are proceeding to PCI unless there is a high risk of life-threatening bleeding or other contraindications.[d]	I	B

Prasugrel si pas de préTx de Clopidogrel et PCI et pas de haut risque de saignement

Ticagrelor pour tout type de SCA

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8 molécules antiplaquettaires en cas de SCA

Le clinicien dispose de recommandations : ESC, ACC/AHA.

Charge Clopidogrel si Ticagrelor ni Prasug

Charge Clopidogrel 600 si PCI prévue

Clopidogrel 150 maintien sur 7 jours si PCI faite

Durée d'arrêt P2Y12 si CABG

Test Clopidogrel non recommandé, mais …

Recommendations	Class	Level
A higher [dose] of clopidogrel 150 mg daily should be c[onsidered] with PCI and [increased] risk of bleeding.		
Increasing the main[tenance] dose of clopidogrel based on platelet fu[nction testing] considered in selected		
Genotyping and/or platelet [function] testing may be considered in selected cases when clopidogrel is used.	IIb	B
In patients pre-treated with $P2Y_{12}$ inhibitors who need to undergo non-emergent major surgery (including CABG), postponing surgery at least for 5 days after cessation of ticagrelor or clopidogrel, and 7 days for prasugrel, if clinically feasible and unless the patient is at high risk of ischaemic events should be considered.	IIa	C
Ticagrelor or clopidogrel should be considered to be (re-) started after CABG surgery as soon as considered safe.	IIa	B
The combination of aspirin with an NSAID (selective COX-2 inhibitors and non-selective NSAID) is not recommended.	III	C

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Trois moments clés et 10 situations pour le choix des antiplaquettaires dans les SCA

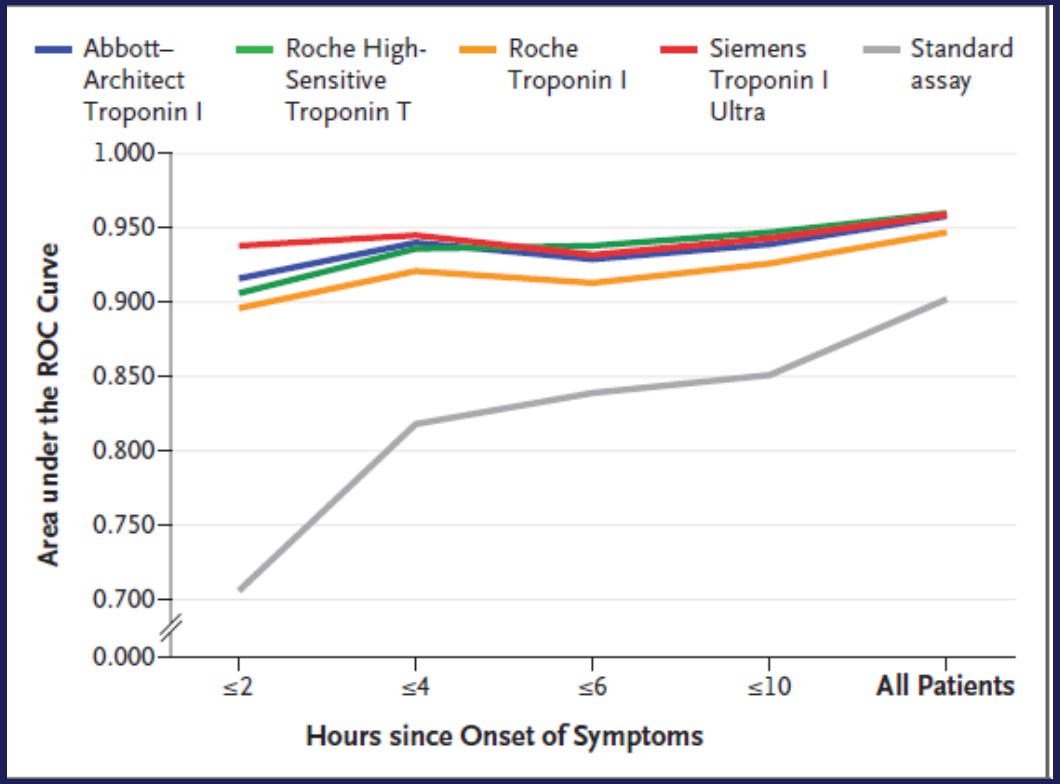
- *Pré hospitalier et admission:*
  1. *Est-ce bien un syndrôme coronarien aigu ?*
  2. *Est-ce un STEMI ou NSTE-ACS ?*
  3. *Si STEMI, Reperfusion ? Par TLYSE ou PCI ?*
  4. *Si NSTE-ACS, stratégie invasive ou conservative ?*
- *En salle de cathétérisme :*
  5. *Thrombus coronaire ?*
  6. *Indication de PAC ?*
  7. *Coronaires saines ?*
  8. *Angioplastie : traitement antiplaquettaire adéquat ?*
- *A l'USIC (ou à la sortie):*
  9. *Risque hémorragique au long terme ?*
  10. *Risque de thrombose de stent ?*

3 moments et 10 questions pour le choix des antiplaquettaires en cas de SCA

Premier Contact Médical

Q#1: SCA non certain ?

Admission USIC, poursuite du diagnostic Pas d'AP



Reichlin NEJM 2009;361:858-67

Table 3 Possible non-acute coronary syndrome causes of troponin elevation (bold: important differential diagnoses)

• **Chronic or acute renal dysfunction**
• Severe congestive **heart failure** – acute and chronic
• **Hypertensive crisis**
• **Tachy- or bradyarrhythmias**
• **Pulmonary embolism**, severe pulmonary hypertension
• Inflammatory diseases, e.g. **myocarditis**
• Acute neurological disease, including **stroke**, or subarachnoid haemorrhage
• Aortic dissection, aortic valve disease or hypertrophic cardiomyopathy
• Cardiac contusion, ablation, pacing, cardioversion, or endomyocardial biopsy
• Hypothyroidism
• Apical ballooning syndrome (Tako-Tsubo cardiomyopathy)
• Infiltrative diseases, e.g. amyloidosis, haemochromatosis, sarcoidosis, sclerodermia
• Drug toxicity, e.g. adriamycin, 5-fluorouracil, herceptin, snake venoms
• Burns, if affecting >30% of body surface area
• Rhabdomyolysis
• Critically ill patients, especially with respiratory failure, or sepsis

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3 moments et 10 questions pour le choix des antiplaquettaires en cas de SCA

Premier Contact Médical

Q#1: SCA non certain ?

Admission USIC, poursuite du diagnostic Pas d'AP

Q#1: SCA est certain ?

Aspirine: orale150-300 ou IV 80-150 mg

$P < 0.001$].[104–106] A loading dose of chewed, plain aspirin between 150 and 300 mg is recommended.[107] I.v. aspirin is an alternative mode of application, but has not been investigated in trials and is not available everywhere. A daily maintenance dose

The use of intravenous formulations of aspirin is considered unnecessary, unless dictated by the inability of the patient to swallow or chew an oral formulation. It should be emphasized that the commonly used intravenous administration of 500 mg of aspirin would achieve systemic drug levels equivalent to ~1000 mg of plain aspirin given orally, thereby producing substantial inhibition of PGI_2 biosynthesis.[79] These considerations should limit the use of intravenous aspirin to 80–150 mg and encourage drug companies to develop an appropriate intravenous formulation of low-dose aspirin.

Hamm ESC guidelines NSTE-ACS, 2011

Patrono, Position paper Eur Heart J 2011;32:2922-32

3 moments et 10 questions pour le choix des antiplaquettaires en cas de SCA

Premier Contact Médical

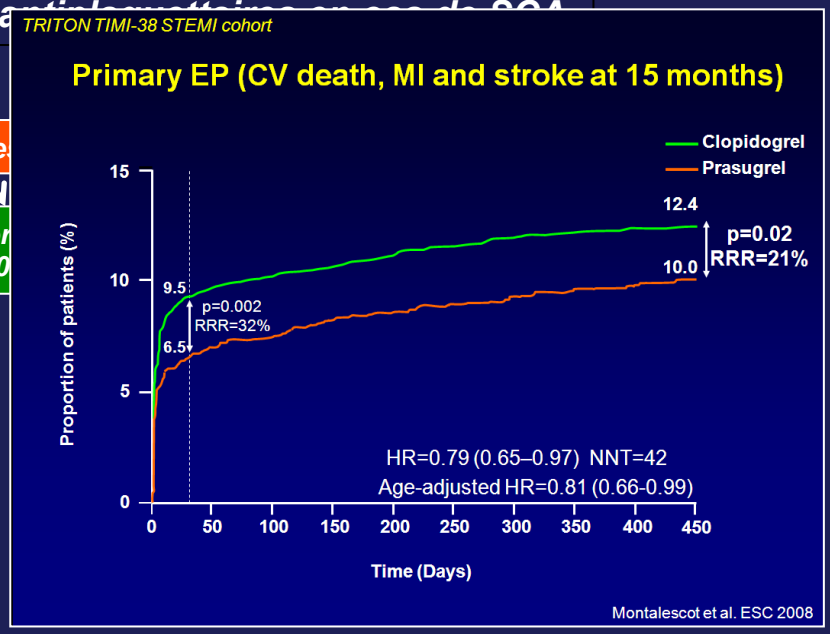
Q#1: SCA non certain ?

Admission USIC, poursuite du diagnostic Pas d'AP

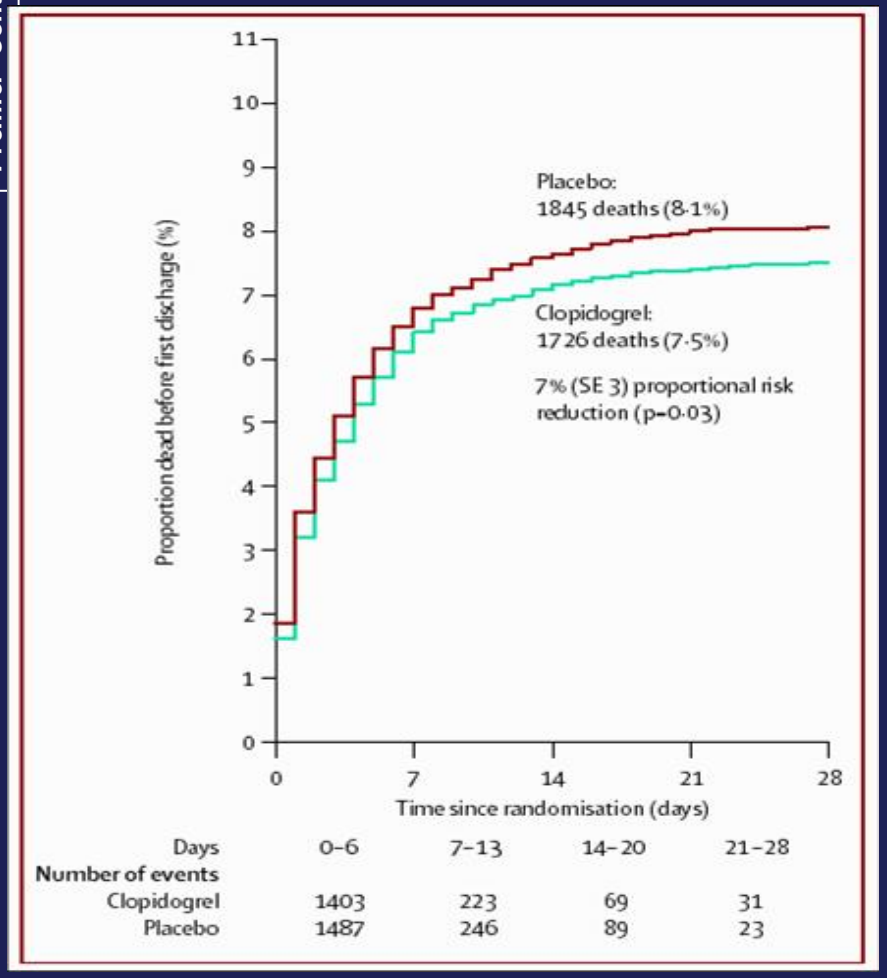
Q#1: SCA e

Q#2: STEMI ?

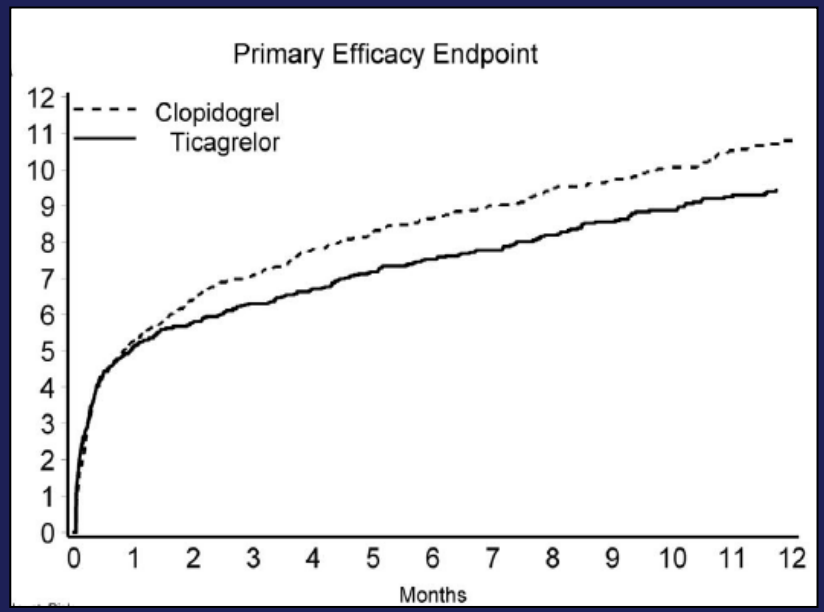
Aspirine: or ou IV 80-150



TRITON Montalescot Lancet 2009



COMMIT CCS 2. Lancet 2005;366:1607-21

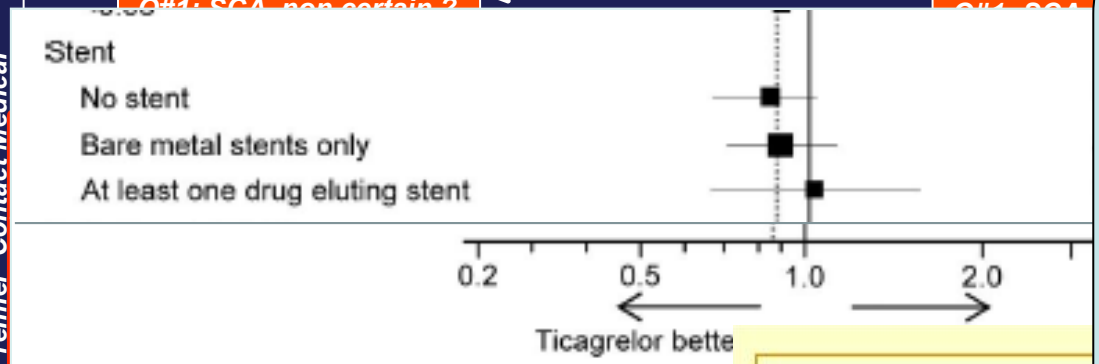


Steg Circulation 2010; 211:2131-41

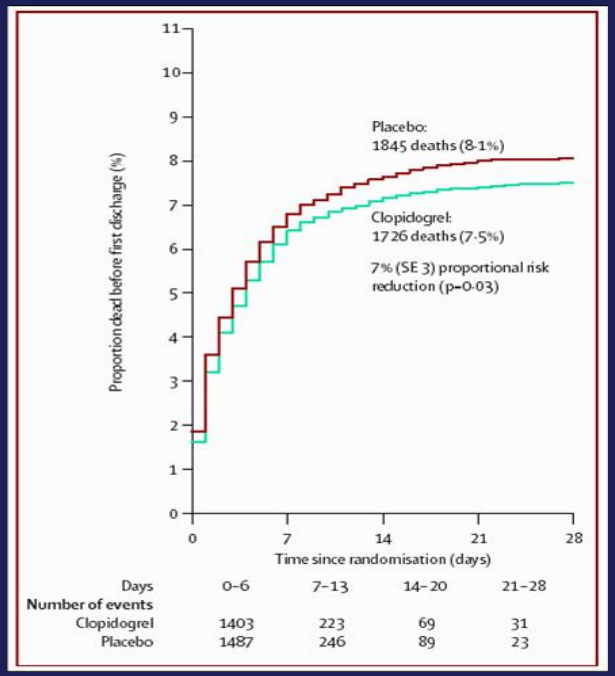
3 moments et 10 questions pour le choix des antiplaquettaires en cas de SCA

Premier Contact Médical

Q#1: SCA non certain ?



Q#1: SCA

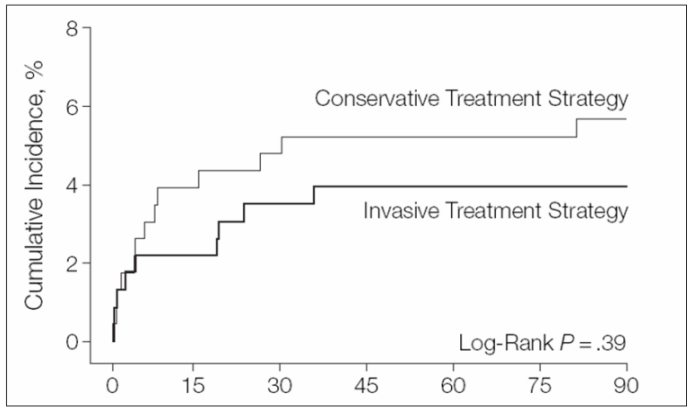


Reperfusi

Recommendations

▪ Indicated in all pts with chest pain/discomfort of < and with persistent ST-segment elevation or (presum new LBBB		A
▪ Should be considered if there is clinical and/or ECG evidence of ongoing ischaemia if symptoms started > 12 h before	a	C
▪ Reperfusion (PCI) in stable pts presenting > 12 h to 24 h after symptom onset	IIb	B
▪ PCI of totally occluded infarct artery in stable pts without signs of ischaemia > 24 h after symptom onset	III	B

Mechanical Reperfusion in Patients With Acute Myocardial Infarction Presenting More Than 12 Hours From Symptom Onset
A Randomized Controlled Trial

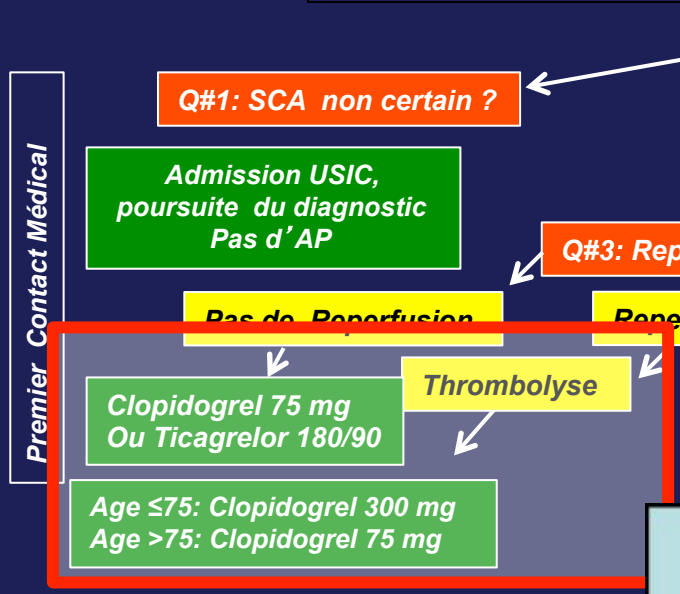


Schomig *JAMA* 2005;293:2865-72

COMMIT CCS 2. Lancet 2005;366:1607-21

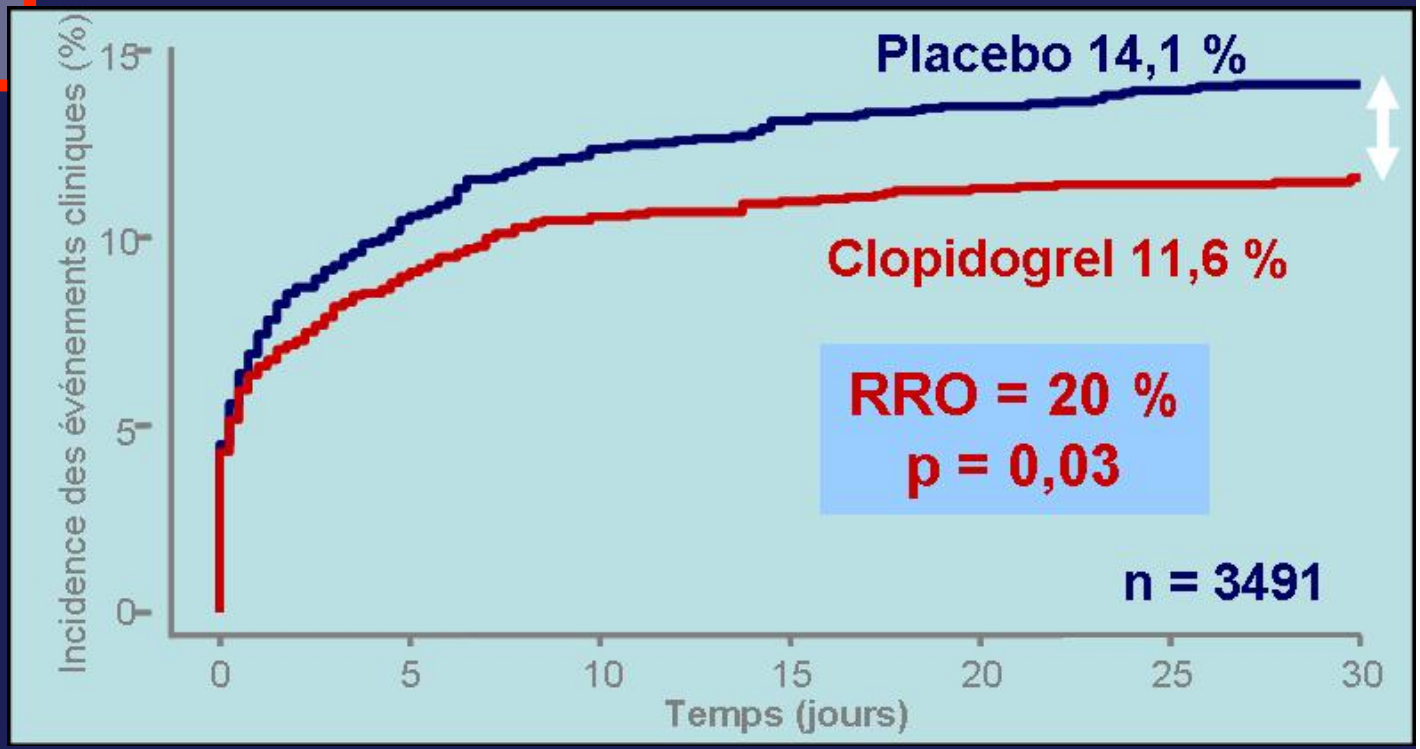
Steg Circulation 2010; 211:2131-41

3 moments et 10 questions pour le choix des antiplaquettaires en cas de SCA



Réduction significative des événements du critère primaire angiographique et clinique

- **Flux TIMI 0/1 (coronarographie avant la sortie de l'hôpital),**
- **Décès ou IDM (avant la coronarographie ou avant la sortie de l'hôpital)**



CLARITY-TIMI 28. N Engl J Med 2005; 352: 1179-89.

3 moments et 10 questions pour le choix des antiplaquettaires en cas de SCA

Premier Contact Médical

Q#1: SCA non certain ?

Admission USIC, poursuite du diagnostic
Pas d'AP

Q#1: SCA es

Aspirine: ora
ou V 80-150

Q#3: Reperfusion?

Pas de Reperfusion

Reperfusion

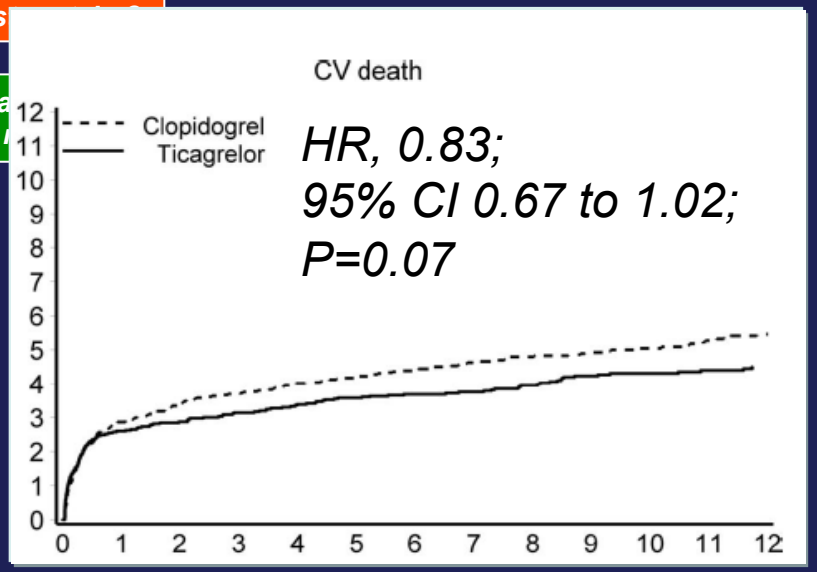
Thrombolyse

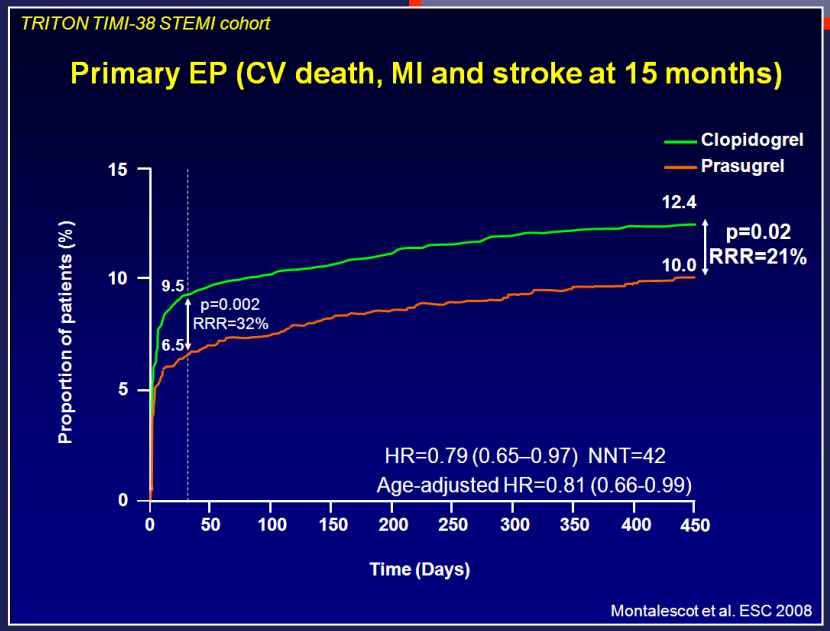
Primary PCI

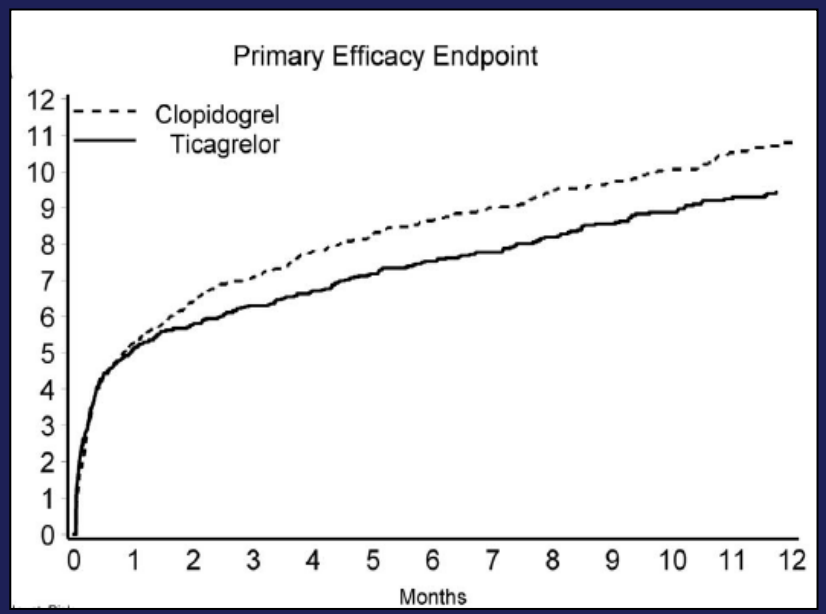
Clopidogrel 75 mg
Ou Ticagrelor 180/mg

Age ≤75: Clopidogrel 300 mg
Age >75: Clopidogrel 75 mg

Prasugrel 60 mg si age<75, poids >60kg, pas d'AVC;
Ou Ticagrelor 180 mg;
ou Clopidogrel 600 mg si haut risque hémorragique







TRITON Montalescot Lancet 2009

Steg Circulation 2010; 211:2131-41

3 moments et 10 questions pour le choix des antiplaquettaires en cas de SCA

Premier Contact Médical

Q#1: SCA non certain ?

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Pas d'AP

Q#1: SCA est certain ?

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Q#3: Reperfusion?

Pas de Reperfusion

Reperfusion

Thrombolyse

Primary PCI

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Ou Ticagrelor 180/mg

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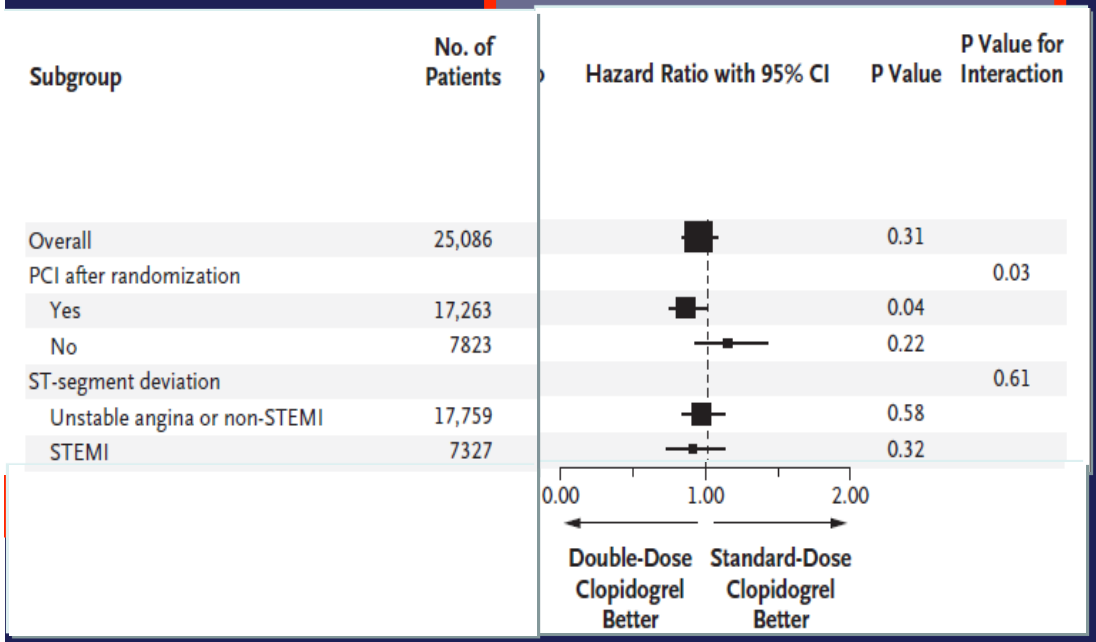
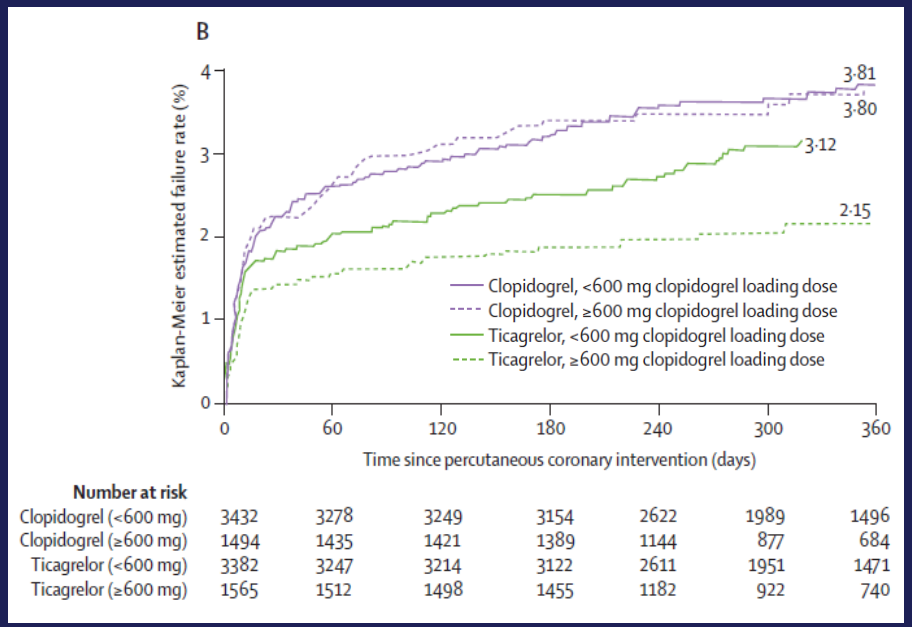
Ou Ticagrelor 180 mg;
ou Clopidogrel 600 mg si haut risque hémorragique



CURRENT-OASIS7 N Engl J Med 2011



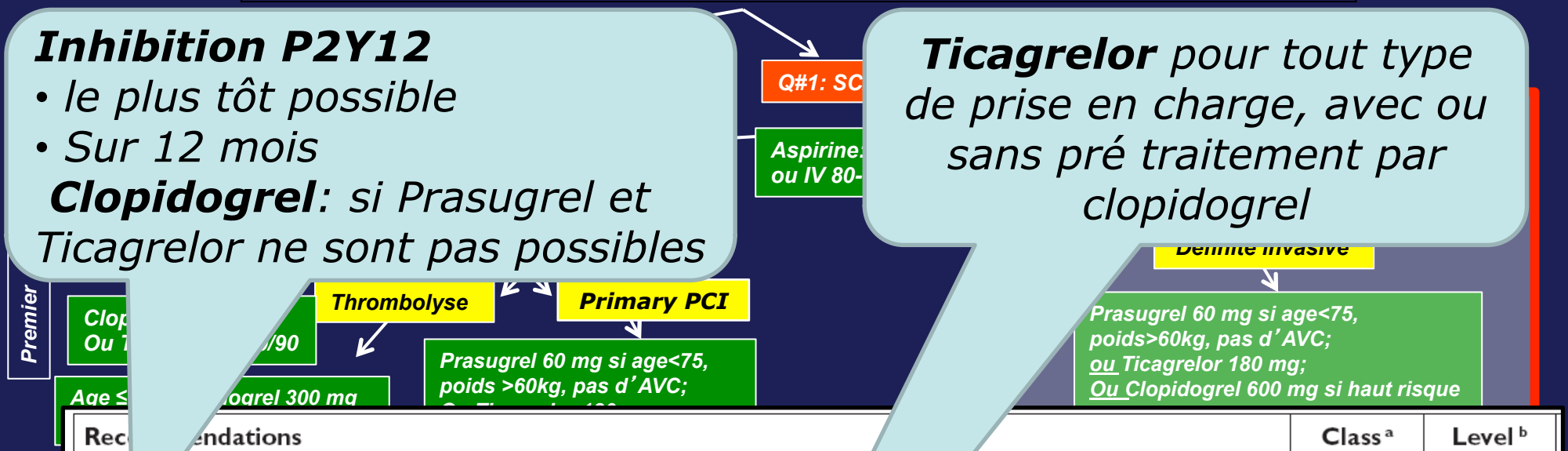
Cannon CP, et al. Lancet. 2010;375:283–293.

3 moments et 10 questions pour le choix des antiplaquettaires en cas de SCA

Inhibition P2Y12
- *le plus tôt possible*
- *Sur 12 mois*

***Clopidogrel**: si Prasugrel et Ticagrelor ne sont pas possibles*

***Ticagrelor** pour tout type de prise en charge, avec ou sans pré traitement par clopidogrel*



Recommendations	Class [a]	Level [b]
Aspirin should be given to all patients without contraindications at an initial l… dose of 150–300 mg, and at a maintenance dose of 75–100 mg daily long-term regardless of treatment str…	I	A
A P2Y$_{12}$ inhibitor should be added to aspirin as soon as possible and main… contraindications such as excessive risk of bleeding.		
A proton pump inhibitor (preferably not omeprazole) in combination … DAP… history of gastrointestinal haemorrhage or peptic ulcer, and appropr… for pa… (*H. elicobacter pylori* infection, age ≥65 years, concurrent use of anti…gulants o…		
Prolonged or permanent withdrawal of P2Y$_{12}$ inhibitors within 1… months after… clinically indicated.		
Ticagrelor (180-mg loading dose, 90 mg twice daily) is recommended for all patients at m… …igh risk of ischaemic events (e.g. elevated troponins) , regardless of initial treatment strategy and i… …those pre-treated with clopidogrel (which should be discontinued when ticagrelor is commenced).	I	B
Prasugrel (60-mg loading dose, 10-mg daily dose) is recommended for P2Y$_{12}$-inhibitor-naïve patients (especially diabetics) in whom coronary anatomy is known and who are proceeding to PCI unless there is a high risk of life-threatening bleeding or other contraindications.[d]	I	B

Prasugrel
- *si pas de préTx de Clopidogrel*
- *Si PCI*
- *Si bas risque de saignement*

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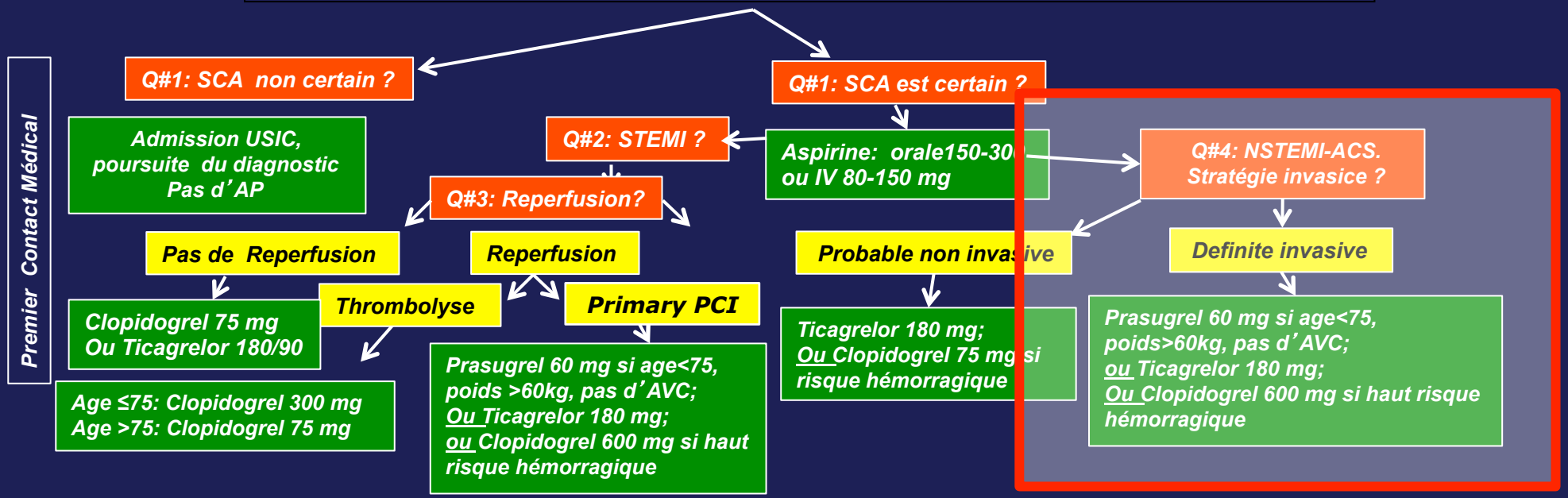
3 moments et 10 questions pour le choix des antiplaquettaires en cas de SCA



Outcome	Double-dose clopidogrel (%)	Standard-dose clopidogrel (%)	HR (95% CI)	p
CV death/MI/stroke*	3.9	4.5	0.86 (0.74-0.99)	0.039
Definite stent thrombosis	0.7	1.3	0.54	0.0001
Major bleeding	1.6	1.1	1.41(1.09-1.83)	0.009

*Primary efficacy end point

Mehta Lancet OASIS 7 invasive 2010

3 moments et 10 questions pour le choix des antiplaquettaires en cas de SCA

Premier Contact Médical

Q#1: SCA non certain ?

Admission USIC, poursuite du diagnostic
Pas d'AP

Q#1: SCA est certain ?

Aspirine: orale150-30
ou IV 80-150 mg

Q#2: STEMI ?

Q#3: Reperfusion?

Pas de Reperfusion

Clopidogrel 75 mg
Ou Ticagrelor 180/90

Age ≤75: Clopidogrel 300 mg
Age >75: Clopidogrel 75 mg

Reperfusion

Thrombolyse

Primary PCI

Prasugrel 60 mg si age<75, poids >60kg, pas d'AVC;
Ou Ticagrelor 180 mg;
ou Clopidogrel 600 mg si haut risque hémorragique

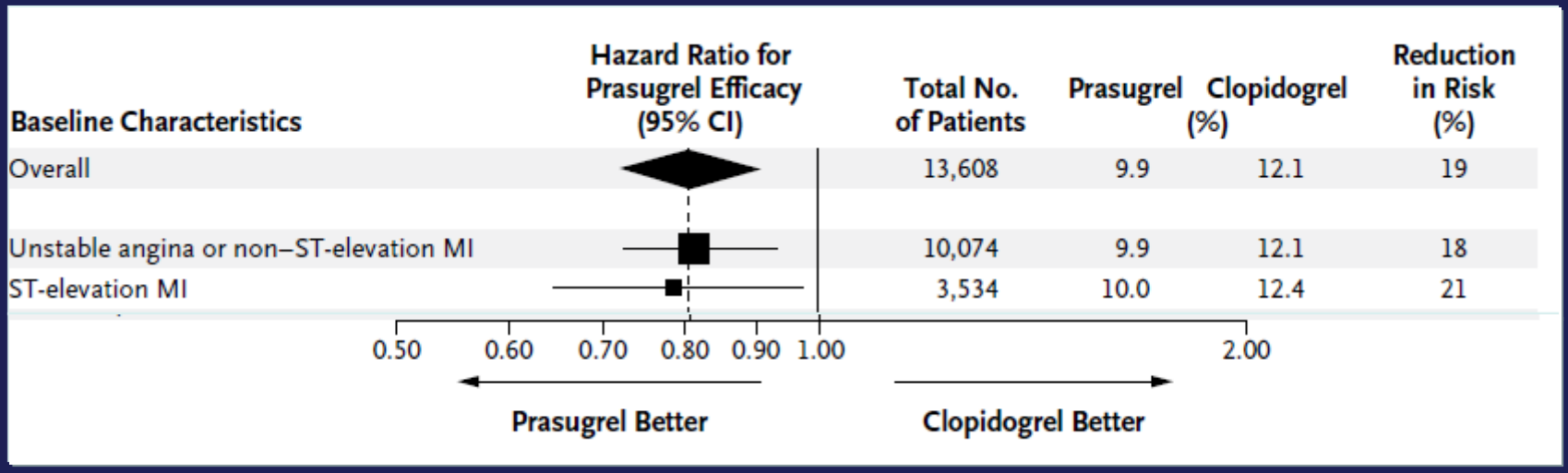
Probable non invasive

Ticagrelor 180 mg;
Ou Clopidogrel 75 mg si risque hémorragique

Q#4: NSTEMI-ACS. Stratégie invasice ?

Definite invasive

Prasugrel 60 mg si age<75, poids>60kg, pas d'AVC;
ou Ticagrelor 180 mg;
Ou Clopidogrel 600 mg si haut risque hémorragique



Wiviott TRITON N Engl J Med 2007;357:20

3 moments et 10 questions pour le choix des antiplaquettaires en cas de SCA

Premier Contact Médical

Q#1: SCA non certain ?

Admission USIC, poursuite du diagnostic
Pas d'AP

Q#1: SCA est certain ?

Aspirine: orale150-300 ou IV 80-150 mg

Q#2: STEMI ?

Q#3: Reperfusion?

Pas de Reperfusion

Clopidogrel 75 mg
Ou Ticagrelor 180/90

Age ≤75: Clopidogrel 300 mg
Age >75: Clopidogrel 75 mg

Reperfusion

Thrombolyse

Primary PCI

Prasugrel 60 mg si age<75, poids >60kg, pas d'AVC;
Ou Ticagrelor 180 mg;
ou Clopidogrel 600 mg si haut

Q#4: NSTEMI-ACS. Stratégie invasice ?

Probable non invasive

Ticagrelor 180 mg;
Ou Clopidogrel 75 mg si risque hémorragique

Definite invasive

Prasugrel 60 mg si age<75, poids>60kg, pas d'AVC;
ou Ticagrelor 180 mg;
Ou Clopidogrel 600 mg si haut risque hémorragique

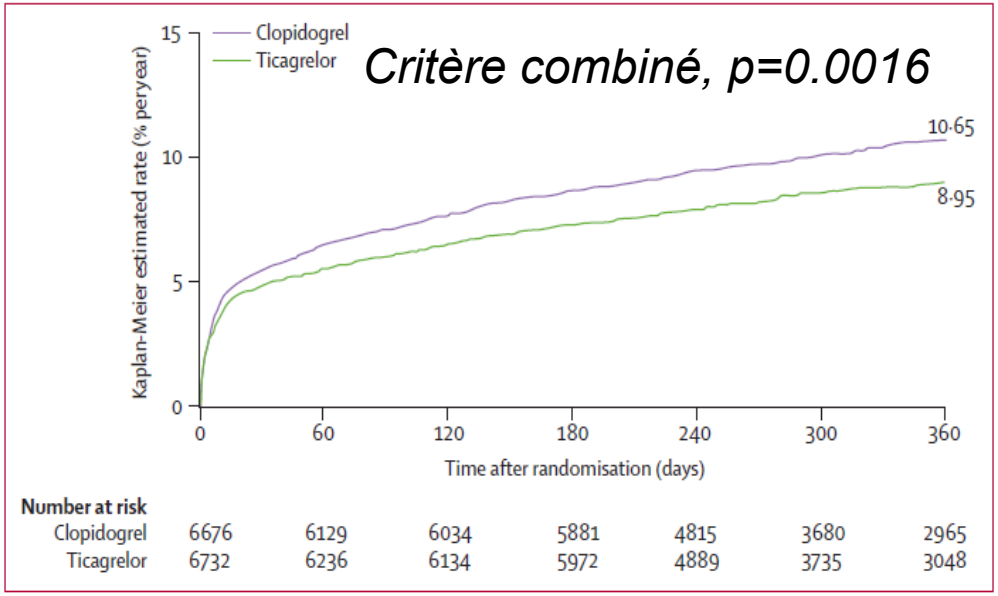
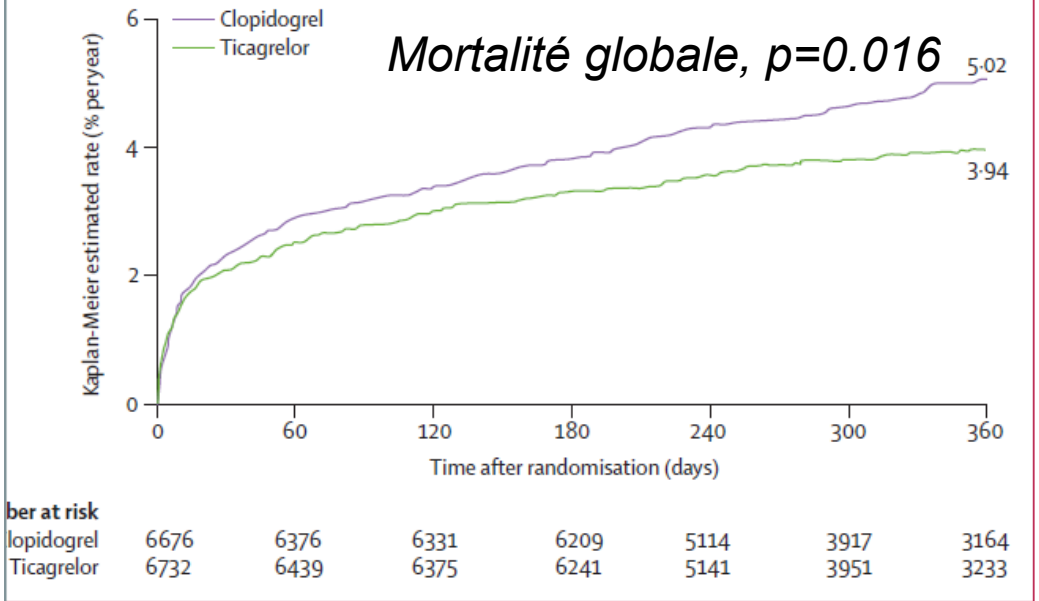


Figure 2: Cumulative Kaplan-Meier estimates of time to first primary efficacy endpoint in patients for whom an invasive strategy was planned



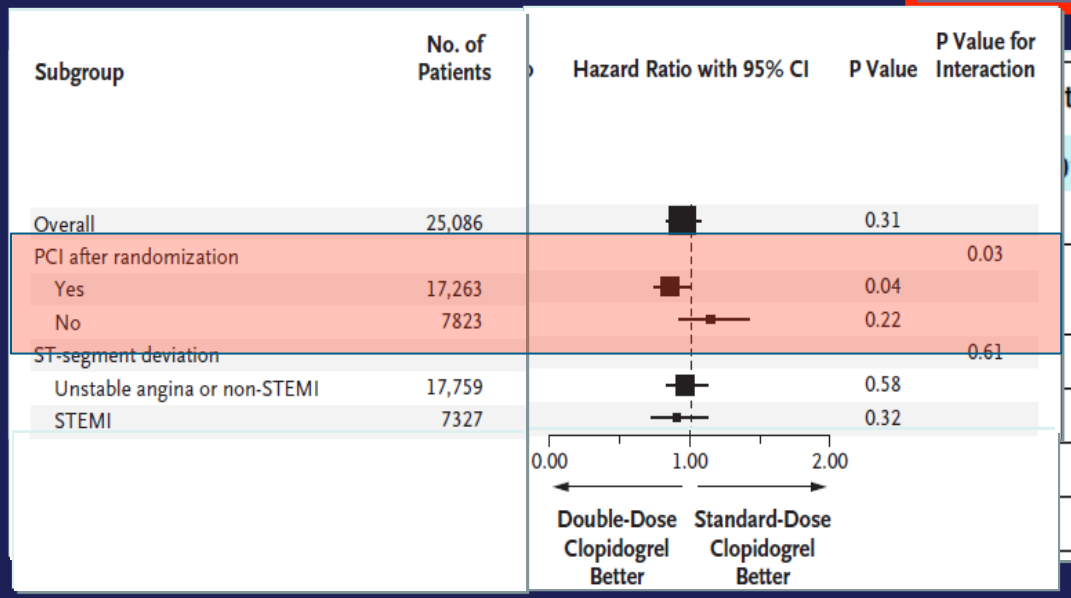
: Cumulative Kaplan-Meier estimates of time to all-cause mortality in patients intended to undergo
sive strategy

Cannon CP, et al. Lancet. 2010;375(9711):283–293.

3 moments et 10 questions pour le choix des antiplaquettaires en cas de SCA

Premier Contact Médical

- Q#1: SCA non certain ?
  - Admission USIC, poursuite du diagnostic Pas d'AP
- Q#1: SCA est certain ?
  - Aspirine: orale150-300 ou IV 80-150 mg
  - Q#2: STEMI ?
    - Q#3: Reperfusion?
      - Pas de Reperfusion
        - Clopidogrel 75 mg Ou Ticagrelor 180/90
        - Thrombolyse
          - Age ≤75: Clopidogrel 300 mg
          - Age >75: Clopidogrel 75 mg
      - Reperfusion
        - Primary PCI
          - Prasugrel 60 mg si age<75, poids >60kg, pas d'AVC; Ou Ticagrelor 180 mg; ou Clopidogrel 600 mg si haut risque hémorragique
    - Probable non invasive
      - Ticagrelor 180 mg; Ou Clopidogrel 75 mg si risque hémorragique
      - Confirmé non invasive
  - Q#4: NSTEMI-ACS. Stratégie invasice ?
    - Definite invasive
      - Prasugrel 60 mg si age<75, poids>60kg, pas d'AVC; ou Ticagrelor 180 mg; Ou Clopidogrel 600 mg si haut risque hémorragique



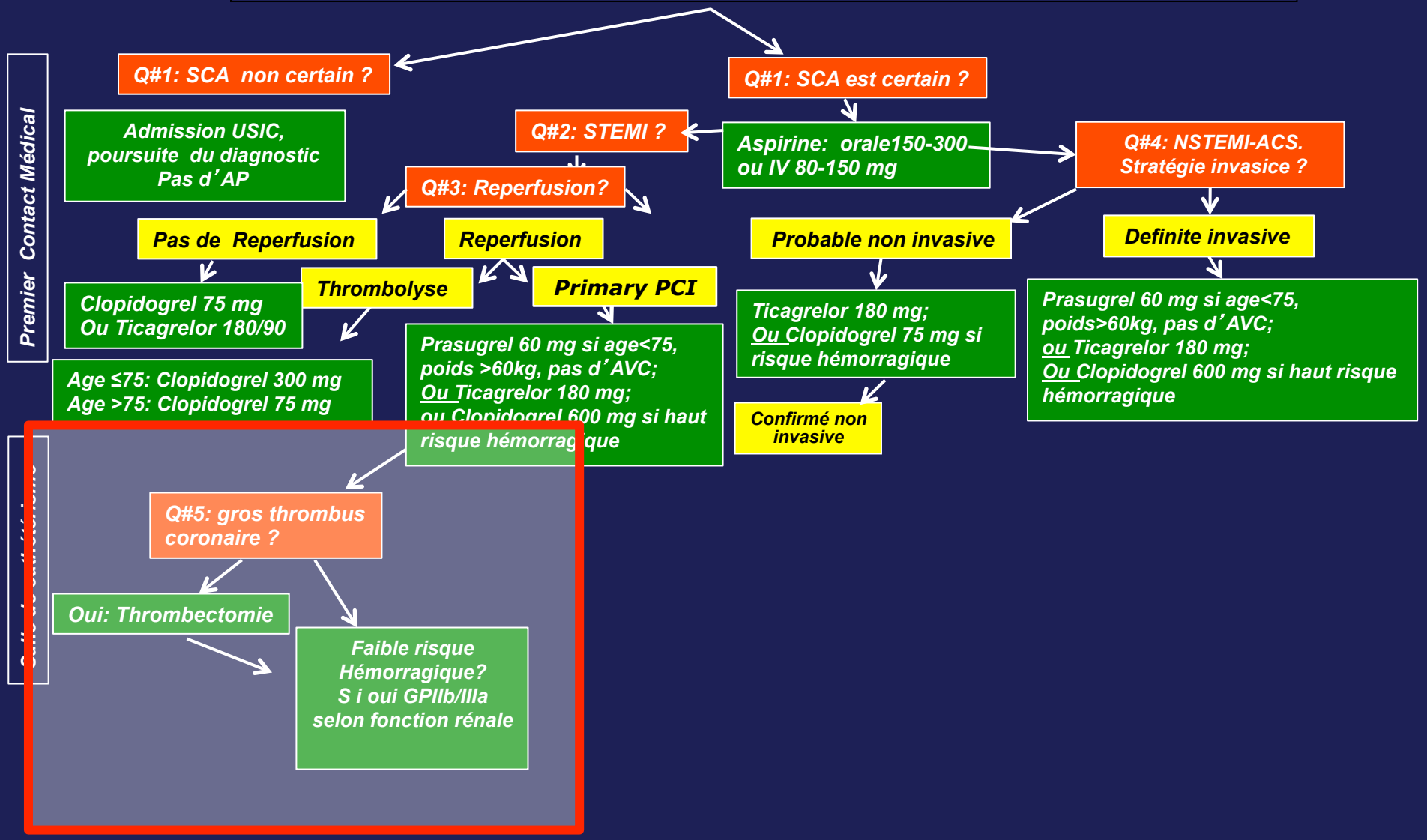
tes of percentage rate of end point (numbers) at 12 months

01)	Clopidogrel (n=2615)	Hazard ratio (95% CI)	P value*
	14.3 (346)	0.85 (0.73 to1.00)	0.045
	7.8 (187)	0.94 (0.77 to 1.15)	0.555
	7.2 (173)	0.76 (0.61 to 0.96)	0.019
	8.2 (195)	0.75 (0.61 to 0.93)	0.010

CURRENT-OASIS7 N Engl J Med 2011

James et al. BMJ 2011;432:d3527.

3 moments et 10 questions pour le choix des antiplaquettaires en cas de SCA



cas de SCA

TABLE 5. Risk of Major Bleeding by Aspirin Dose in Various Patient Subgroups

	≤100 mg, % (n)	101 to 199 mg, % (n)	≥200 mg, % (n)	P Value for Trend
PCI alone	1.9 (997)	2.4 (508)	3.9 (1000)	0.0068
CABG	6.9 (829)	7.6 (514)	11.1 (728)	0.0030
No revascularization	1.5 (3494)	2.2 (2087)	2.3 (2382)	0.019
Heparin	2.6 (4774)	3.2 (2909)	4.4 (3910)	<0.0001
No heparin	0.9 (546)	2.0 (200)	1.5 (200)	0.39
GP IIb/IIIa	5.4 (298)	1.7 (115)	5.1 (410)	0.96
No GP IIb/IIIa	2.2 (5022)	3.2 (2994)	4.2 (3700)	<0.0001

Table 3. Thrombolysis in Myocardial Infarction (TIMI) Bleeding End Points in the Overall Cohort at 15 Months.*

End Point	Prasugrel (N=6741)	Clopidogrel (N=6716)	Hazard Ratio for Prasugrel (95% CI)	P Value
	no. of patients (%)			
Non–CABG-related TIMI major bleeding (key safety end point)	146 (2.4)	111 (1.8)	1.32 (1.03–1.68)	0.03
Related to instrumentation	45 (0.7)	38 (0.6)	1.18 (0.77–1.82)	0.45
Spontaneous	92 (1.6)	61 (1.1)	1.51 (1.09–2.08)	0.01
Related to trauma	9 (0.2)	12 (0.2)	0.75 (0.32–1.78)	0.51
Life-threatening†	85 (1.4)	56 (0.9)	1.52 (1.08–2.13)	0.01
Related to instrumentation	28 (0.5)	18 (0.3)	1.55 (0.86–2.81)	0.14
Spontaneous	50 (0.9)	28 (0.5)	1.78 (1.12–2.83)	0.01
Related to trauma	7 (0.1)	10 (0.2)	0.70 (0.27–1.84)	0.47
Fatal‡	21 (0.4)	5 (0.1)	4.19 (1.58–11.11)	0.002
Nonfatal	64 (1.1)	51 (0.9)	1.25 (0.87–1.81)	0.23
Intracranial	19 (0.3)	17 (0.3)	1.12 (0.58–2.15)	0.74
Major or minor TIMI bleeding	303 (5.0)	231 (3.8)	1.31 (1.11–1.56)	0.002
Bleeding requiring transfusion§	244 (4.0)	182 (3.0)	1.34 (1.11–1.63)	<0.001
CABG-related TIMI major bleeding¶	24 (13.4)	6 (3.2)	4.73 (1.90–11.82)	<0.001

Peter Circulation 2003;108:1682

Wiviott N Engl J Med 2007;357:20

Q#4: NSTEMI-ACS. tratégie invasice ?

Definite invasive

60 mg si age<75, kg, pas d'AVC; elor 180 mg; logrel 600 mg si haut risque ique

Q#6: Surgery ?

Stop P2Y12: Clopidogrel ou ticagrelor 5 jours avant; prasugrel 7 jours avant. Reprendre DAPT Ticagrelor + aspirine

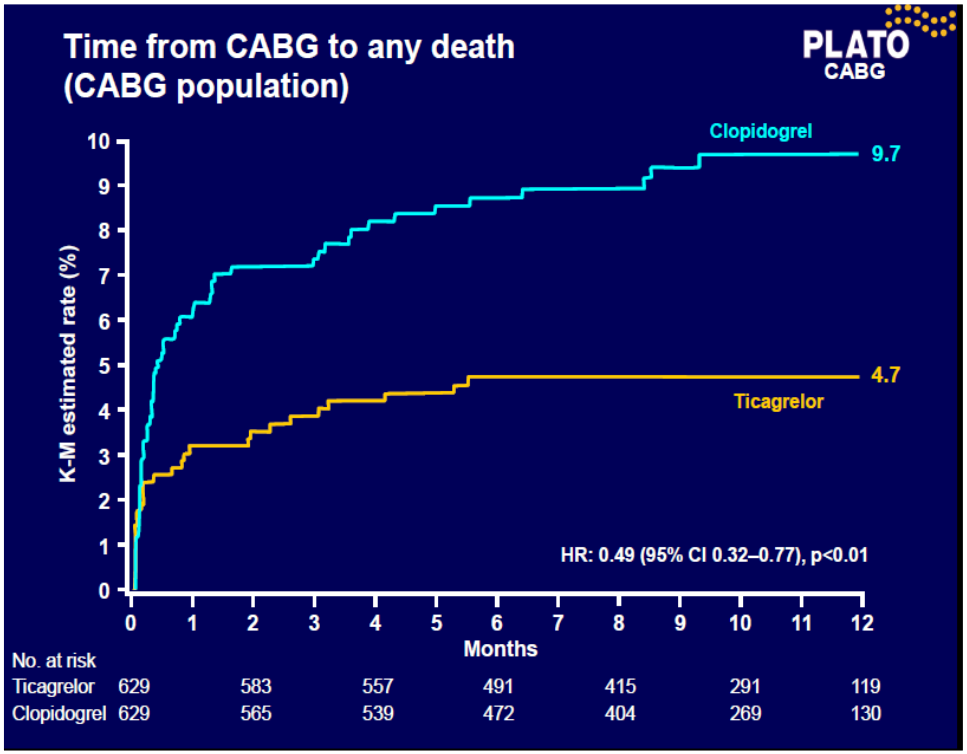
3 moments et 10 questions pour le choix des antiplaquettaires en cas de SCA

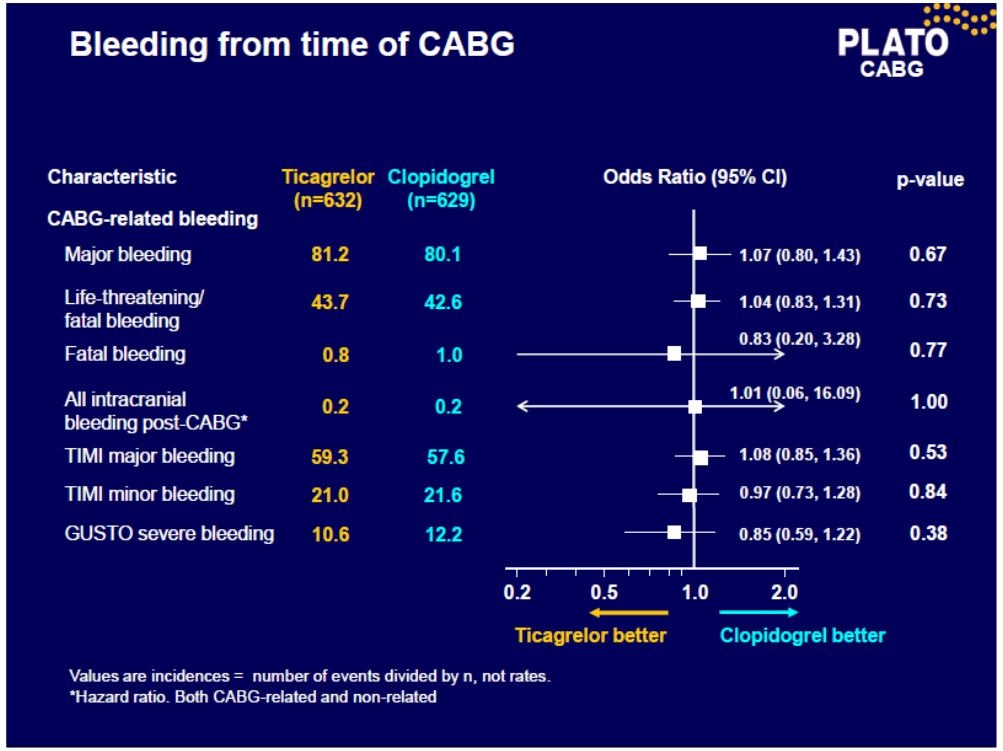
Q#1: SCA non certain ?

Q#1: SCA est certain ?

Admission USIC

Q#2: STEMI ?



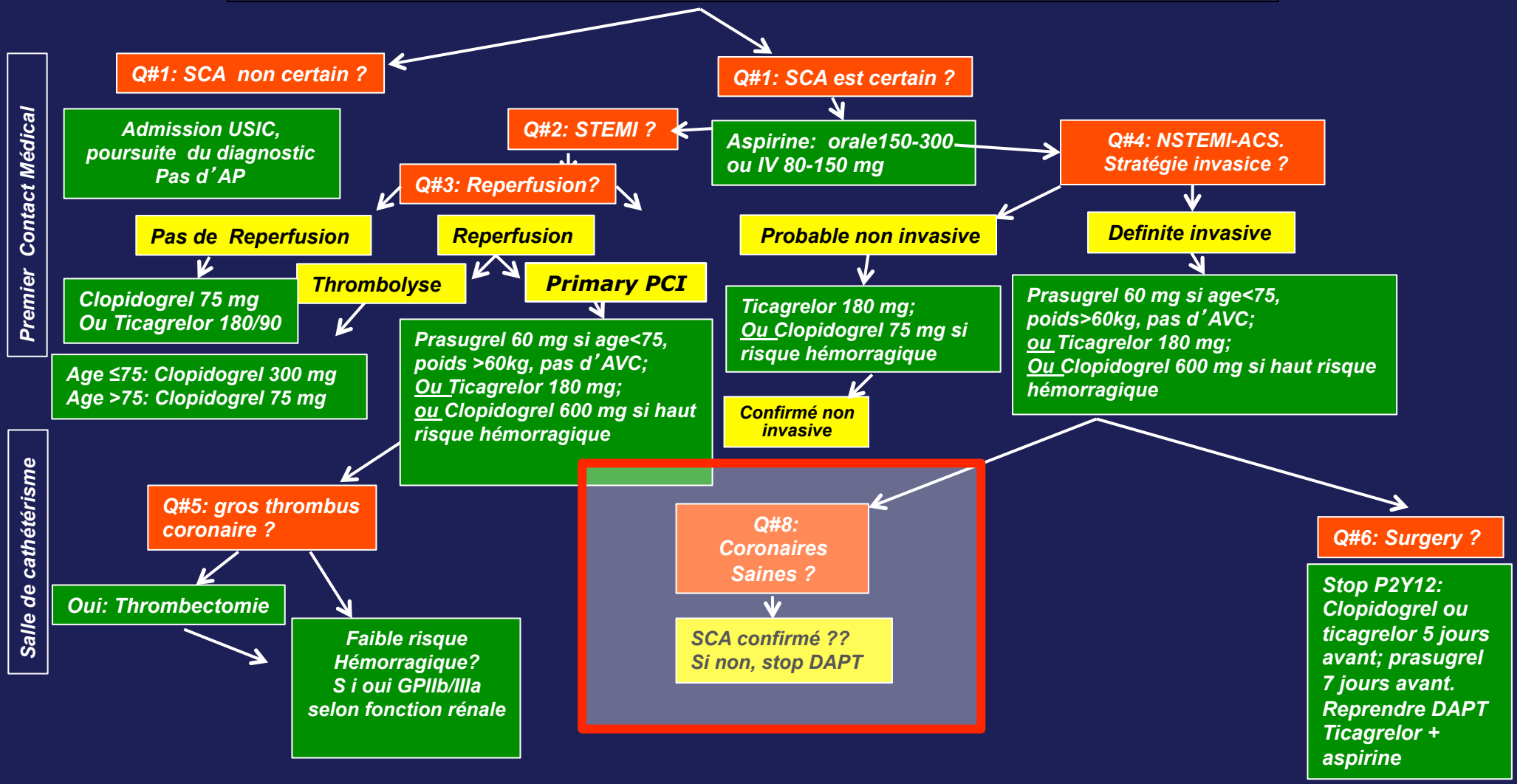


Ticagrelor + aspirine

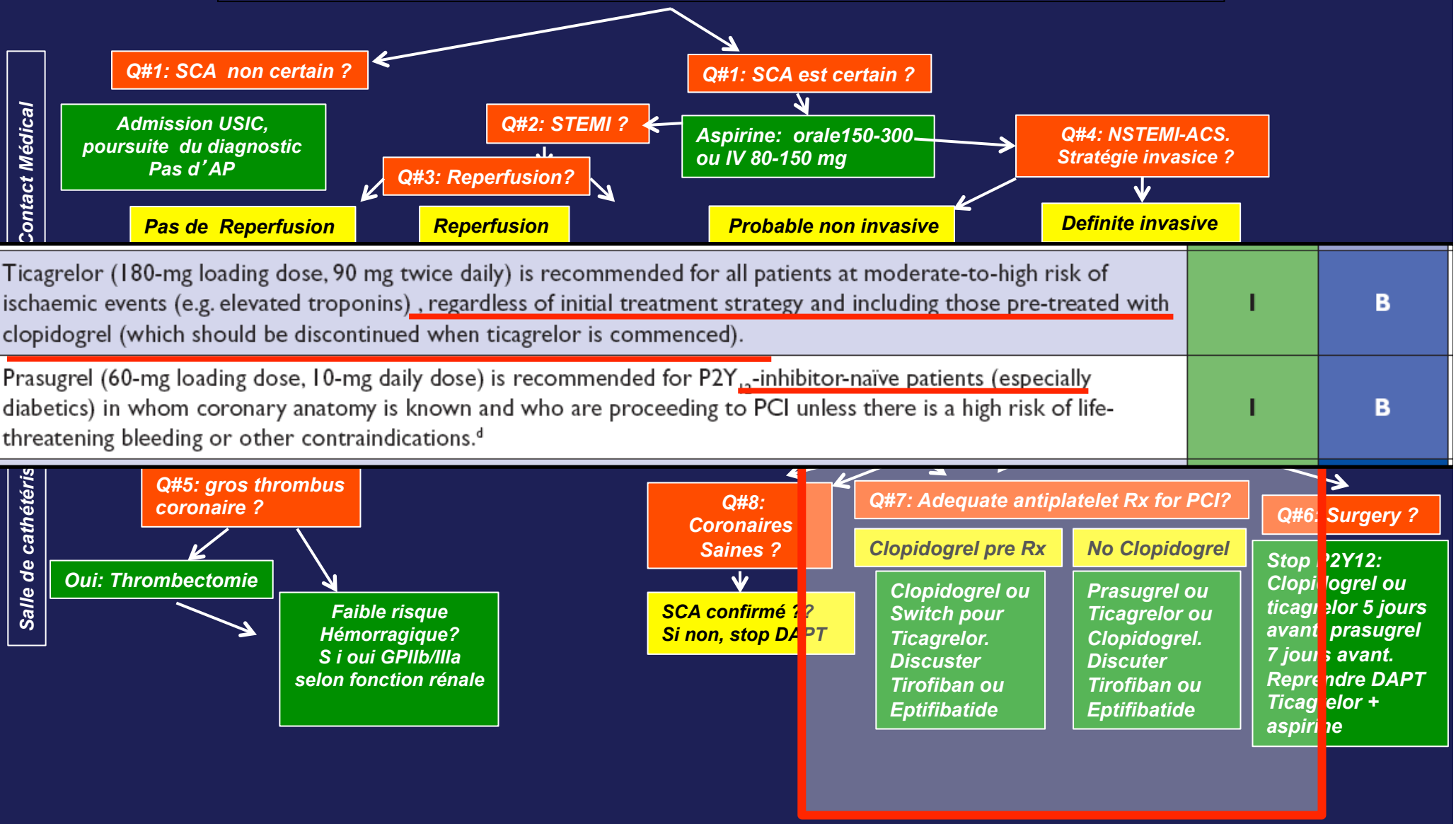
PLATO: patients soumis à pontage

- sous groupe pré défini
- arrêt Ticagrelor: 3-5j avant PAC puis reprise
- réduction de mortalité toutes causes
- réduction des saignements

3 moments et 10 questions pour le choix des antiplaquettaires en cas de SCA

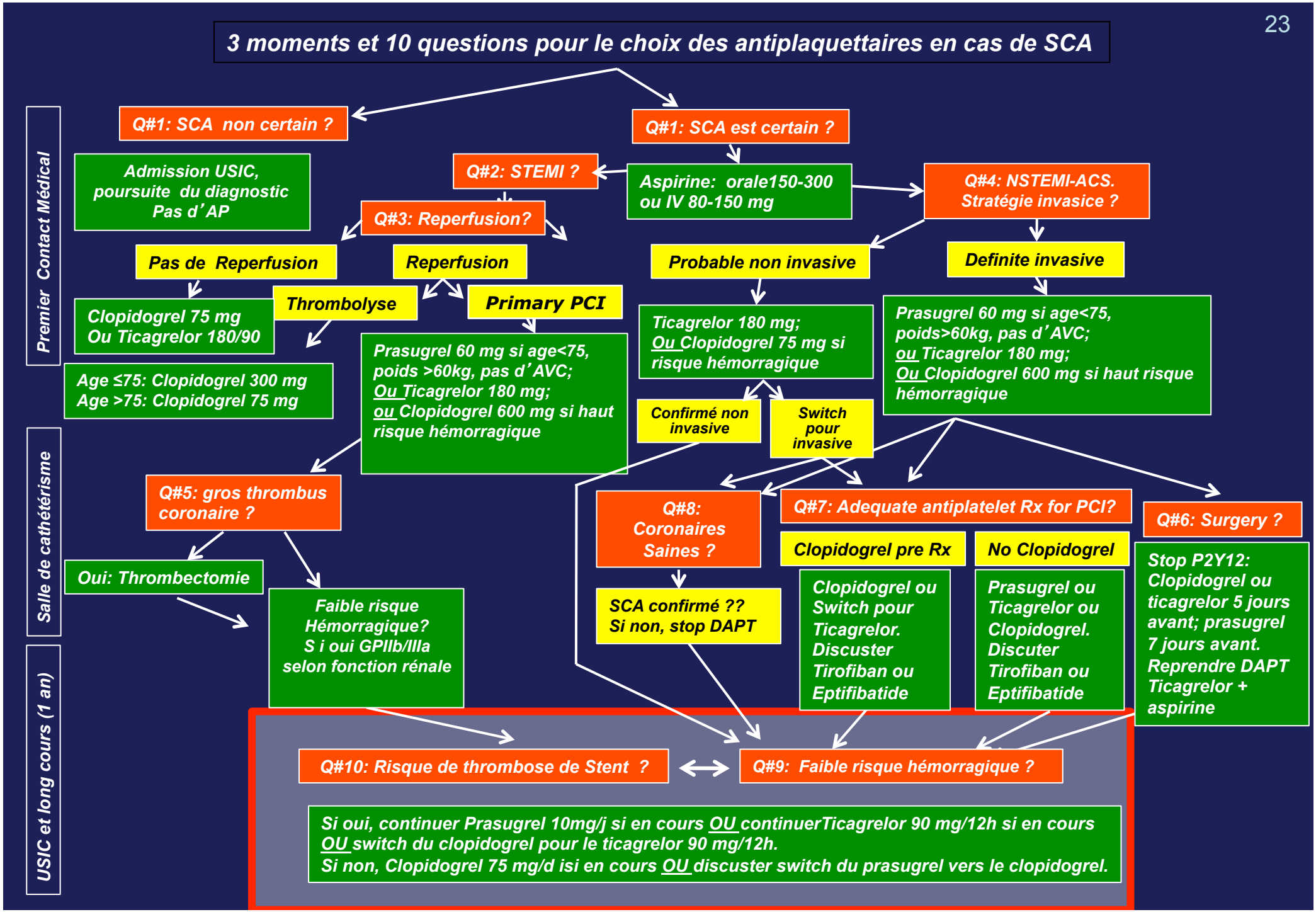


3 moments et 10 questions pour le choix des antiplaquettaires en cas de SCA



Hamm ESC guidelines NSTE-ACS, 2011

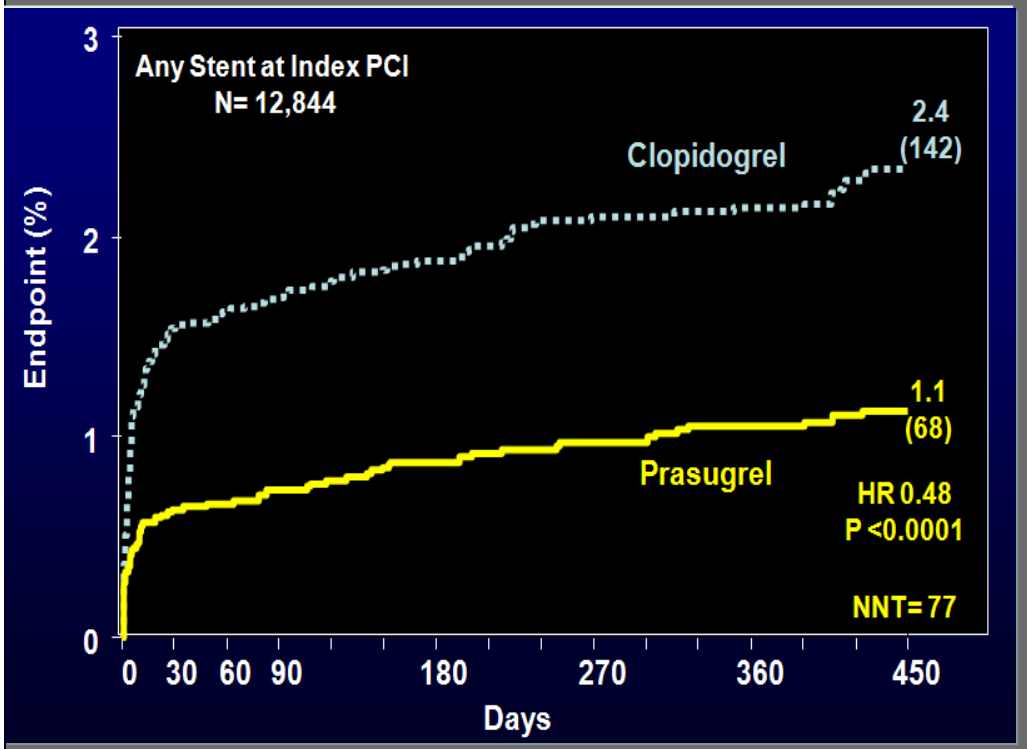
3 moments et 10 questions pour le choix des antiplaquettaires en cas de SCA



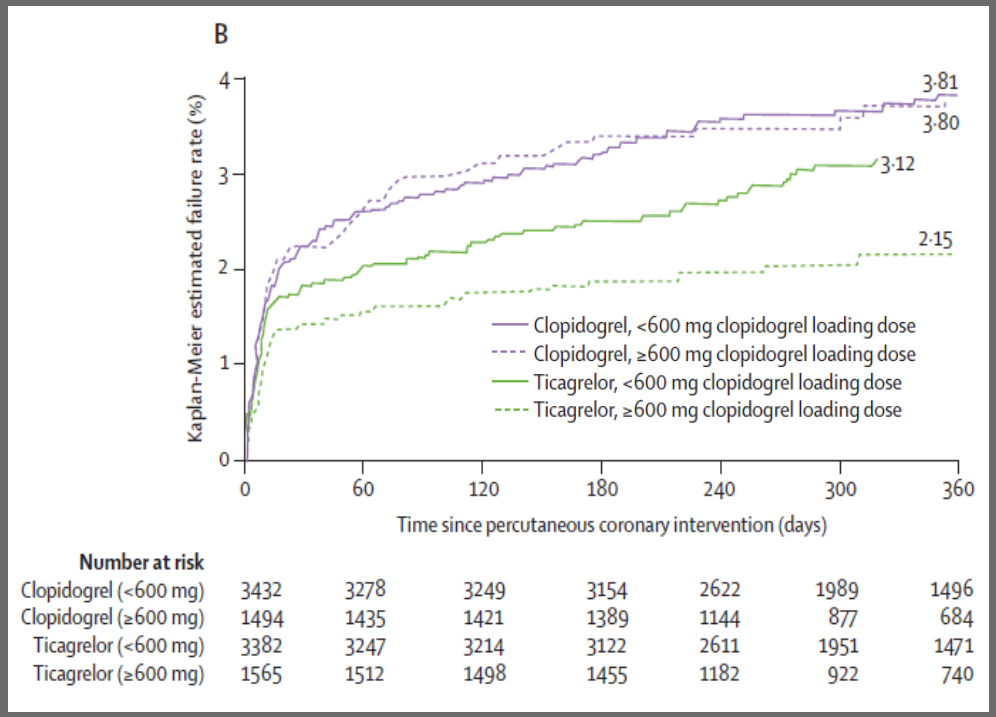
3 moments et 10 questions pour le choix des antiplaquettaires en cas de SCA

Q#1: SCA non certain ?

Q#1: SCA est certain ?



Wiviott N Engl J Med 2007;357:20



Number at risk							
Clopidogrel (<600 mg)	3432	3278	3249	3154	2622	1989	1496
Clopidogrel (≥600 mg)	1494	1435	1421	1389	1144	877	684
Ticagrelor (<600 mg)	3382	3247	3214	3122	2611	1951	1471
Ticagrelor (≥600 mg)	1565	1512	1498	1455	1182	922	740

Cannon Lancet. 2010;375:283–293.

USIC et long cours (1 a

Eptifibatide

Eptifibatide

aspirine

Q#10: Risque de thrombose de Stent ? ⟷ **Q#9: Faible risque hémorragique ?**

Si oui, continuer Prasugrel 10mg/j si en cours OU continuer Ticagrelor 90 mg/12h si en cours OU switch du clopidogrel pour le ticagrelor 90 mg/12h.
Si non, Clopidogrel 75 mg/d si en cours OU discuter switch du prasugrel vers le clopidogrel.