SCA à haut risque:

Optimisation de l'association anticoagulants-antiagrégants
Les Recommandations 2010

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Biarritz le 09/06/2011

Conflits d'intérêt: consultant pour Medicine Company

Guidelines on myocardial revascularization 2010

The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)

Recommandations

ESC 2010

NSTE-ACS			
Antiplatelet therapy			
	ASA	I	C
	Clopidogrel (with 600 mg loading dose as soon as possible)	I	C
	Clopidogrel (for 9–12 months after PCI)	I	B
	Prasugrel[d]	IIa	B
	Ticagrelor[d]	I	B
	+ GPIIb–IIIa antagonists (in patients with evidence of high intracoronary thrombus burden)		
	Abciximab (with DAPT)	I	B
	Tirofiban, Eptifibatide	IIa	B
	Upstream GPIIb–IIIa antagonists	III	B
Anticoagulation			
Very high-risk of ischaemia[e]	UFH (+GPIIb–IIIa antagonists) or	I	C
	Bivalirudin (monotherapy)	I	B
Medium-to-high-risk of ischaemia[e]	UFH	I	C
	Bivalirudin	I	B
	Fondaparinux	I	B
	Enoxaparin	IIa	B
Low-risk of ischaemia[e]	Fondaparinux	I	B
	Enoxaparin	IIa	B

Nouvelle classification des SCA

SCA à haut Risque

SCA à très haut risque

Scores

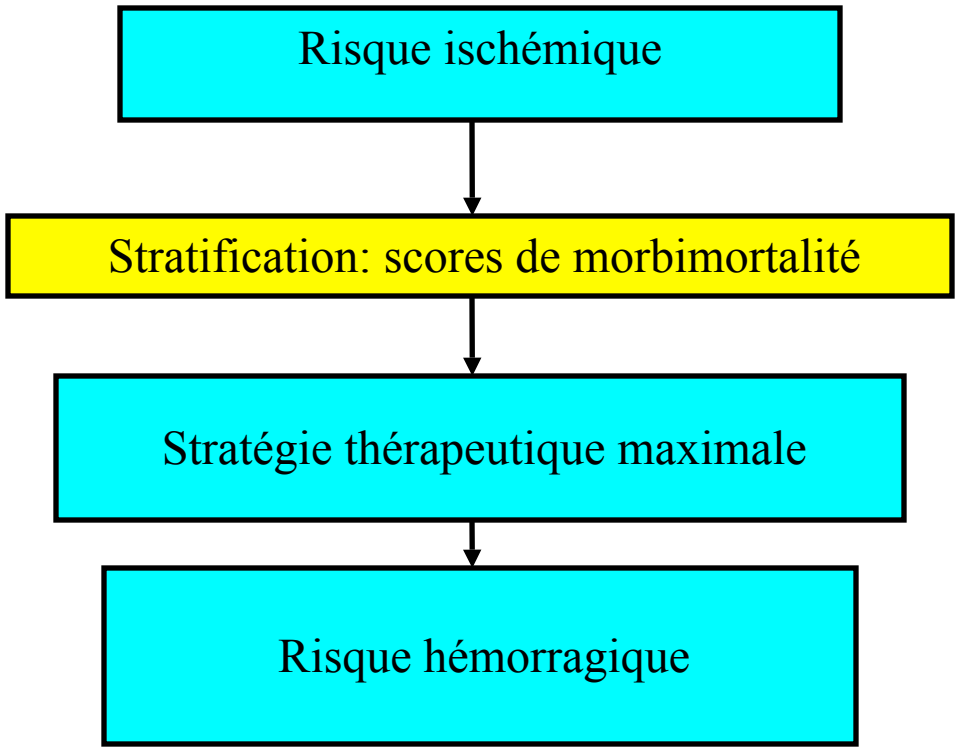
Risques hémorragiques

Grace

Prise en charge des SCA ST-

- Groupe très hétérogène de patients
- Pronostic (après 1 mois) équivalent à celui des STEMI à 1 an
- Importance de la stratification précoce individuelle des risques

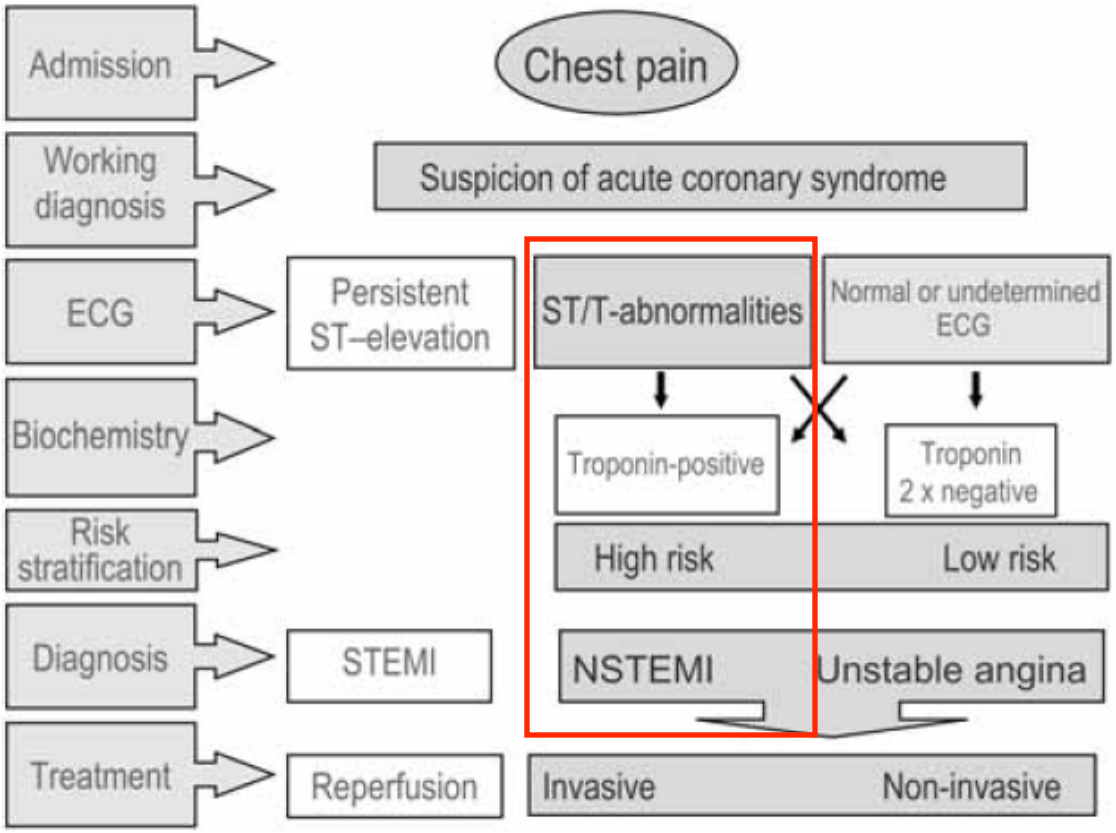
Evaluation personnalisée du risque



Intérêts des scores

- **Les scores de risque ischémique**, (haut risque et très haut risque) couplé au **score GRACE** de morbi-mortalité conditionnent le délai de réalisation des explorations invasives.
- **Les scores de risque hémorragique** conditionnent les associations thérapeutiques anticoagulantes et antiagrégantes

les recommandations 2007
SCA à haut risque



Les recommandations 2010
SCA à très haut et haut risque ischémique

Table 11 Indicators predicting high thrombotic risk or high-risk for progression to myocardial infarction, which indicate emergent coronary angiography

Ongoing or recurrent ischaemia.
Dynamic spontaneous ST changes (>0.1 mV depression or transient elevation).
Deep ST depression in anterior leads V2–V4 indicating ongoing posterior transmural ischaemia.
Haemodynamic instability.
Major ventricular arrhythmia.

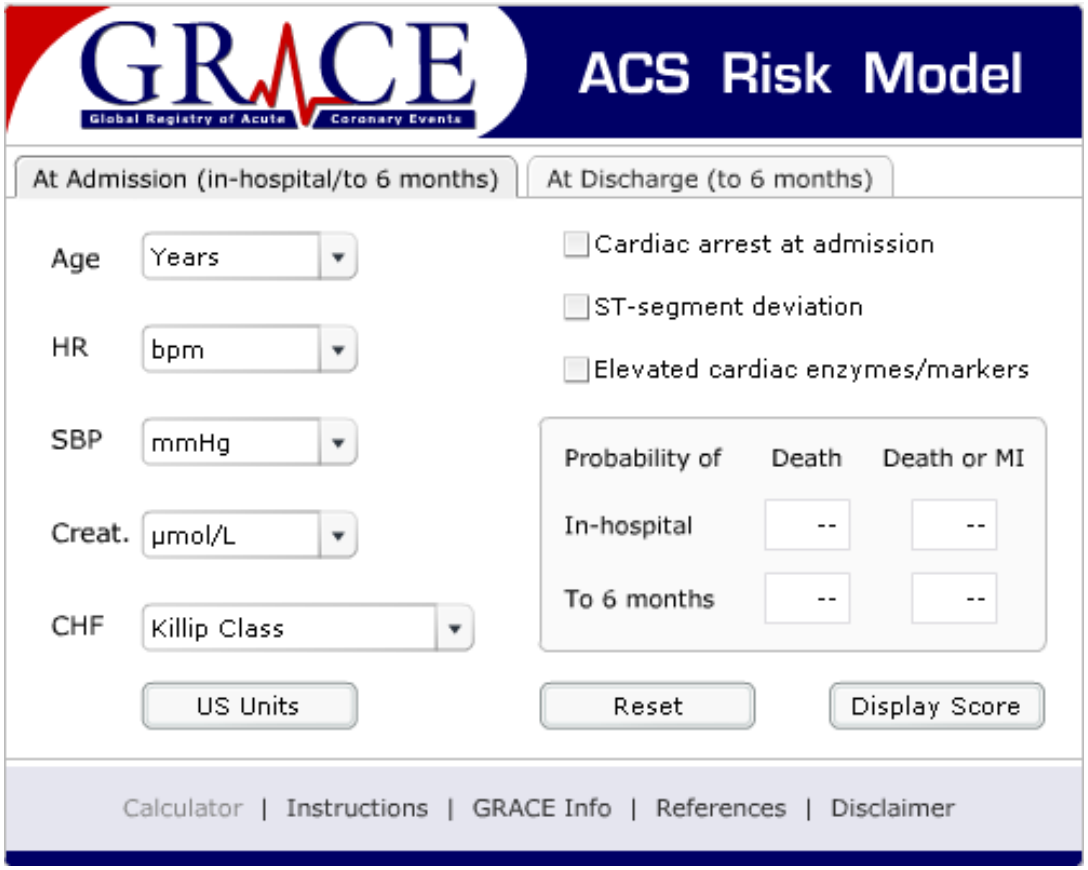
Variations du ST,
Élévation de la troponine,
Diabète,
Hypotension,
BMI élevé,

Risque immédiat et à long terme de décès et évènements cardiovasulaires

Intérêt des scores de morbimortalité: GRACE score

Specification	Class[a]	Level[b]	Ref.[c]
An invasive strategy is indicated in patients with: • GRACE score >140 or at least one high-risk criterion. • recurrent symptoms. • inducible ischaemia at stress test.	I	A	64, 68–70
An early invasive strategy (<24 h) is indicated in patients with GRACE score >140 or multiple other high-risk criteria.	I	A	63, 64, 66, 70–72
A late invasive strategy (within 72 h) is indicated in patients with GRACE score <140 or absence of multiple other high-risk criteria but with recurrent symptoms or stress-inducible ischaemia.	I	A	59, 66, 68
Patients at very high ischaemic risk (refractory angina, with associated heart failure, arrhythmias or haemodynamic instability) should be considered for emergent coronary angiography (<2 h).	IIa	C	—
An invasive strategy should not be performed in patients: • at low overall risk. • at a particular high-risk for invasive diagnosis or intervention.	III	A	59, 68

Global Registry of Acute Coronary Events (GRACE)



http://www.outcomes-umassmed.org/grace/acs_risk/acs_risk_content.html

GRACE score

Table 5 Mortality in hospital and at 6 months in low-, intermediate-, and high-risk categories in registry populations according to the GRACE risk score[8,117]

Risk category (tertiles)	GRACE risk score	In-hospital deaths (%)
Low	≤108	<1
Intermediate	109–140	1–3
High	>140	>3

Risk category (tertiles)	GRACE risk score	Post-discharge to 6 months deaths (%)
Low	≤88	<3
Intermediate	89–118	3–8
High	>118	>8

For calculations, see http://www.outcomes.org/grace.

Revascularisation des SCA ST-

Table 11 Indicators predicting high thrombotic risk or high-risk for progression to myocardial infarction, which indicate emergent coronary angiography

Ongoing or recurrent ischaemia.
Dynamic spontaneous ST changes (>0.1 mV depression or transient elevation).
Deep ST depression in anterior leads V2–V4 indicating ongoing posterior transmural
Haemodynamic insta
Major ventricular arr

Très haut risque:
URGENCE

Haut risque: Score de **GRACE >140**
⇒ exploration dans les 24 h

Haut risque: Score de **GRACE <140**
⇒ exploration dans les 72 h

« Heart team »

		ACS			Stable MVD	Stable with indication for *ad hoc* PCI[a]
	Shock	**STEMI**	**NSTE - ACS[b]**	**Other ACS[c]**		
Multidisciplinary decision making	Not mandatory.	Not mandatory.	Not required for culprit lesion but required for non-culprit vessel(s).	Required.	Required.	According to predefined protocols.
Informed consent	Oral witnessed informed consent or family consent if possible without delay.	Oral witnessed informed consent may be sufficient unless written consent is legally required.	Written informed consent[d] (if time permits).	Written informed consent[d]	Written informed consent[d]	Written informed consent[d]
Time to revascularization	Emergency: no delay.	Emergency: no delay.	Urgency: within 24 h if possible and no later than 72 h.	Urgency: time constraints apply.	Elective: no time constraints.	Elective: no time constraints.
Procedure	Proceed with intervention based on best evidence/ availability.	Proceed with intervention based on best evidence/ availability.	Proceed with intervention based on best evidence/ availability. Non-culprit lesions treated according to institutional protocol.	Proceed with intervention based on best evidence/ availability. Non-culprit lesions treated according to institutional protocol.	Plan most appropriate intervention allowing enough time from diagnostic catheterization to intervention.	Proceed with intervention according to institutional protocol defined by local Heart Team.

Risques hémorragiques: Classifications des saignements

Table 7 Elements of the TIMI[380] and GUSTO[381] bleeding definitions

TIMI bleeding classification[380]	
Major	Intracranial haemorrhage or clinically overt bleeding (including imaging) $\geq$5 g/dL decrease in the haemoglobin concentration
Minor	Clinically overt bleeding (including imaging) with 3 to $<$5 g/dL decrease in the haemoglobin concentration
Minimal	Clinically overt bleeding (including imaging) with a $<$3 g/dL decrease in the haemoglobin concentration
GUSTO bleeding classification[381]	
Severe or life threatening	Either intracranial haemorrhage or bleeding that causes haemodynamic compromise and requires intervention
Moderate	Bleeding that requires blood transfusion but does not result in haemodynamic compromise
Mild	Bleeding that does not meet criteria for either severe or moderate bleeding

All TIMI definitions take into account blood transfusions, such that haemoglobin values are adjusted by 1 g/dL for each unit of packed red blood transfused.

Critères de risques hémorragiques:

Table 8 Multivariate model for major bleeding in patients with non-ST-elevation myocardial infarction[379]

Variable	Adjusted OR	95% CI	*P*-value
Age (per 10-year increase)	1.22	1.10–1.35	0.0002
Female sex	1.36	1.07–1.73	0.0116
History of renal insufficiency	1.53	1.13–2.08	0.0062
History of bleeding	2.18	1.14–4.08	0.014
Mean arterial pressure (per 20 mmHg decrease)	1.14	1.02–1.27	0.019
Diuretics	1.91	1.46–2.49	<0.0001
LMWH only	0.68	0.50–0.92	0.012
LMWH and UFH[a]	0.72	0.52–0.98	0.035
GP IIb/IIIa inhibitors only	1.86	1.43–2.43	<0.0001
Thrombolytics and GP IIb/IIIa inhibitors	4.19	1.68–10.4	0.002
IV inotropic agents	1.88	1.35–2.62	0.0002
Right-heart catheterization	2.01	1.38–2.91	0.0003

[a]Referent groups: male gender; UFH for LMWH only, both LMWH and UFH, and neither LMWH nor UFH; neither thrombolytics nor GP IIb/IIIa inhibitors for thrombolytics only, GP IIb/IIIa inhibitors only, and both thrombolytics and GP IIb/IIIa inhibitors; no for other variables. Hosmer–Lemeshow goodness-of-fit test $P = 0.70$; C-statistic = 0.73.

Facteurs de risque hémorragique

- Facteurs généraux
  - Age > 75 ans
  - Anémie
  - Insuffisance rénale
  - Sexe féminin
  - Poids < 60 kgs ou BMI < 20
  - Troubles de l'hémostase et thrombocytopénie
  - Traitement antérieur par des agents AAP et trithérapie antithrombotique
- Saignements gastro-intestinaux
  - Atcd d'hémorragies digestives
  - Atcd d'ulcère gastroduodénaux
  - Traitement au long cours par AINS
  - Polypes intestinaux
- Saignements intracraniens
  - Atcd d'avc ou ait
  - HTA

Sexe féminin,
age > 75,
antécédents d'hémorragies,
Débit de filtration glomérulaire < 30 ml/mn
Abord artériel fémoral

Un SCA à haut risque?

- Mme X, 81 présente une douleur thoracique spontanée de durée environ 20 mn, elle consulte aux urgences
- ECG normal, la troponine T est a 2.22 à la 6°heure TA 18/9 FC 72 killip 1
- Patiente hypertendue sous trithérapie (Coaprovel et Amlor), créatinémie= 150
- Score de GRACE ?
- Risque hémorragique?

157

Femme, > 65 ans,HTA, insuffisance rénale,

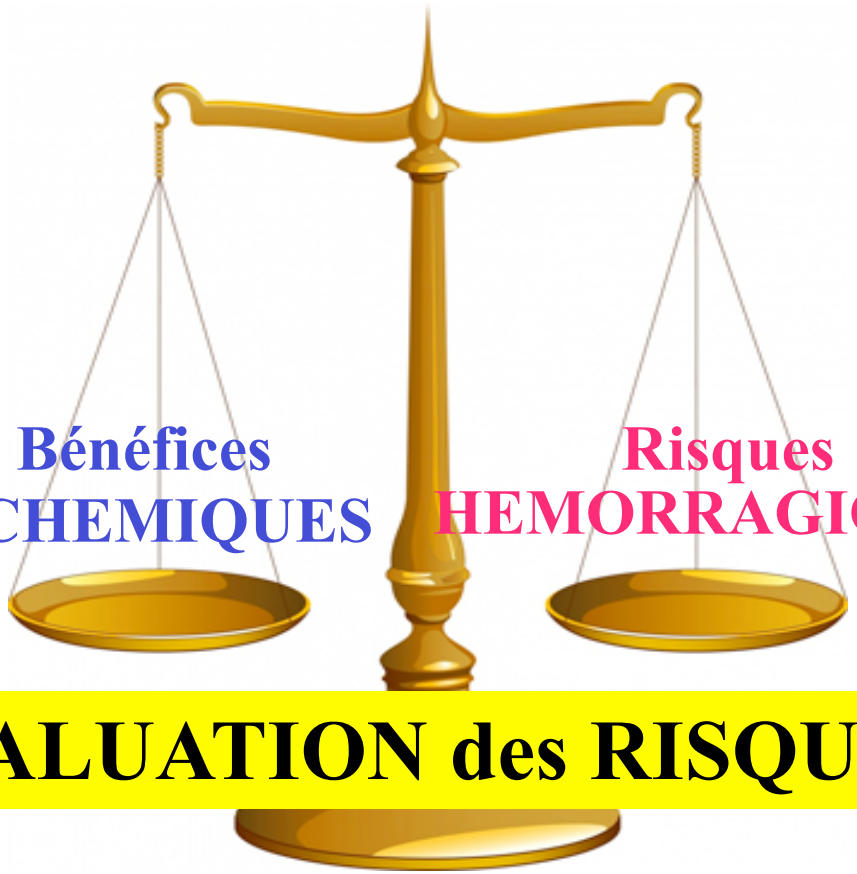
Bilan du SCA à haut risque:

- En fonction des scores de **gravité de risque ischémique**, les explorations invasives sont programmées:
  - Immédiatement (I-C),
  - Dans les 24 heures,
  - Et dans tous les cas, au mieux, dans les 72 premières heures (I-A);

- En tenant compte des **scores de risque hémorragique**, le délai de prise en charge conditionne le choix des traitements anticoagulants et antiagrégants

Prise en charge thérapeutique:

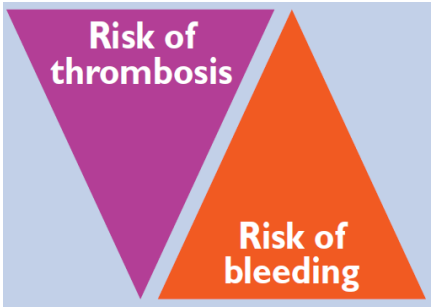
Bénéfices ischémiques et risques hémorragiques



EVALUATION des RISQUES

Enjeux de la prise en charge

- **Balance** entre risques hémorragiques et bénéfices anti-ischémiques des thérapeutiques: un des grands défis de la recherche clinique des prochaines années;



- Les risques hémorragiques conditionnent le pronostic:
  - une transfusion de produit sanguin en phase hospitalière accroît le risque de décès de 4 à 5* à 1 mois et 6 mois

Recommandations
sur les traitements antiagrégants

NSTE-ACS			
Antiplatelet therapy			
	ASA	I	C
	Clopidogrel (with 600 mg loading dose as soon as possible)	I	C
	Clopidogrel (for 9–12 months after PCI)	I	B
	Prasugrel[d]	IIa	B
	Ticagrelor[d]	I	B
	+ GPIIb–IIIa antagonists (in patients with evidence of high intracoronary thrombus burden)		
	Abciximab (with DAPT)	I	B
	Tirofiban, Eptifibatide	IIa	B
	Upstream GPIIb–IIIa antagonists	III	B
Anticoagulation			
Very high-risk of ischaemia[e]	UFH (+GPIIb–IIIa antagonists) or	I	C
	Bivalirudin (monotherapy)	I	B
Medium-to-high-risk of ischaemia[e]	UFH	I	C
	Bivalirudin	I	B
	Fondaparinux	I	B
	Enoxaparin	IIa	B
Low-risk of ischaemia[e]	Fondaparinux	I	B
	Enoxaparin	IIa	B

Recommandations
sur les traitements antiagrégants

- Double anti-agrégation plaquettaire:
  - Aspirine (I-C):
    - Charge: 250-500 mg IV ou 150-300 mg per os puis 75-100 mg per os quotidiens
  - Clopidogrel (I-C):
    - Charge: 600 mg puis 75 mg par jour
  - Prasugrel (IIa-B):
    - Charge: 60 mg puis dose quotidienne de 10 mg
  - Ticagrelor (I-B):
    - Charge: 180 mg puis 90 mg *2 quotidiens

L'Aspirine…I-C

Baisse de 20% des décès et récidives

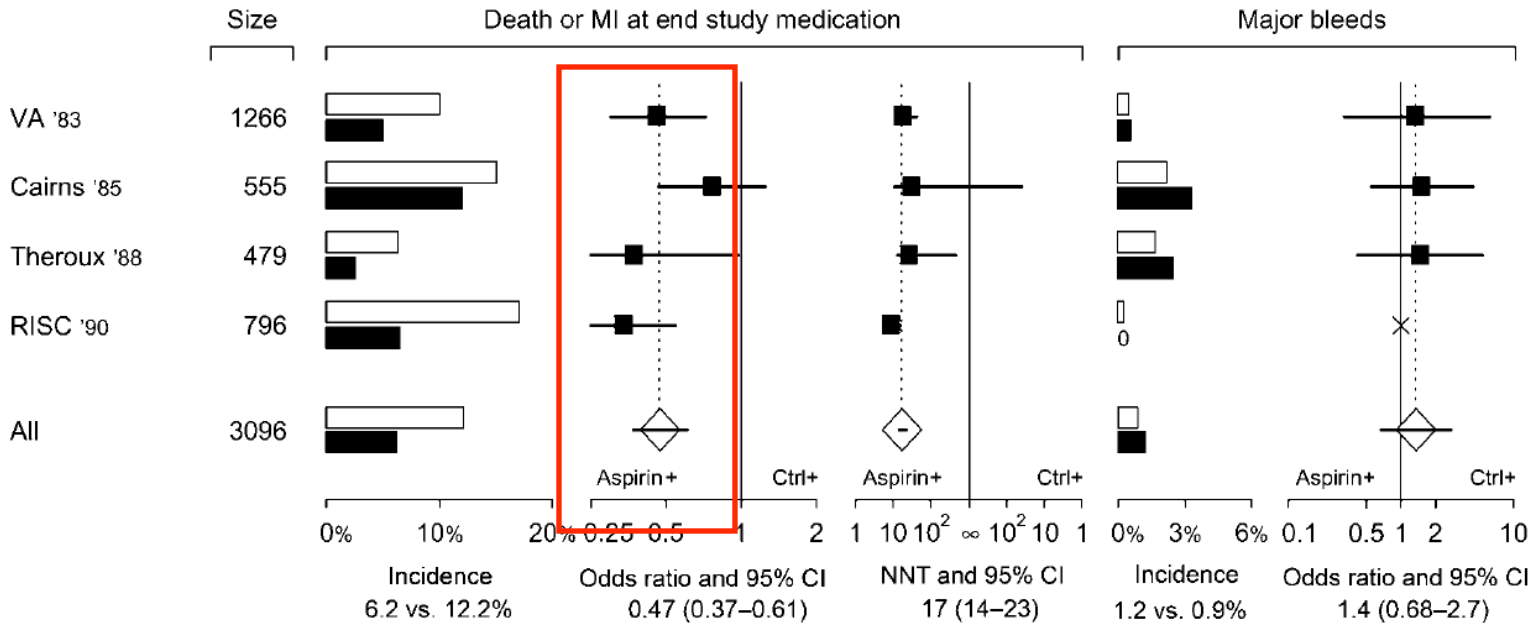
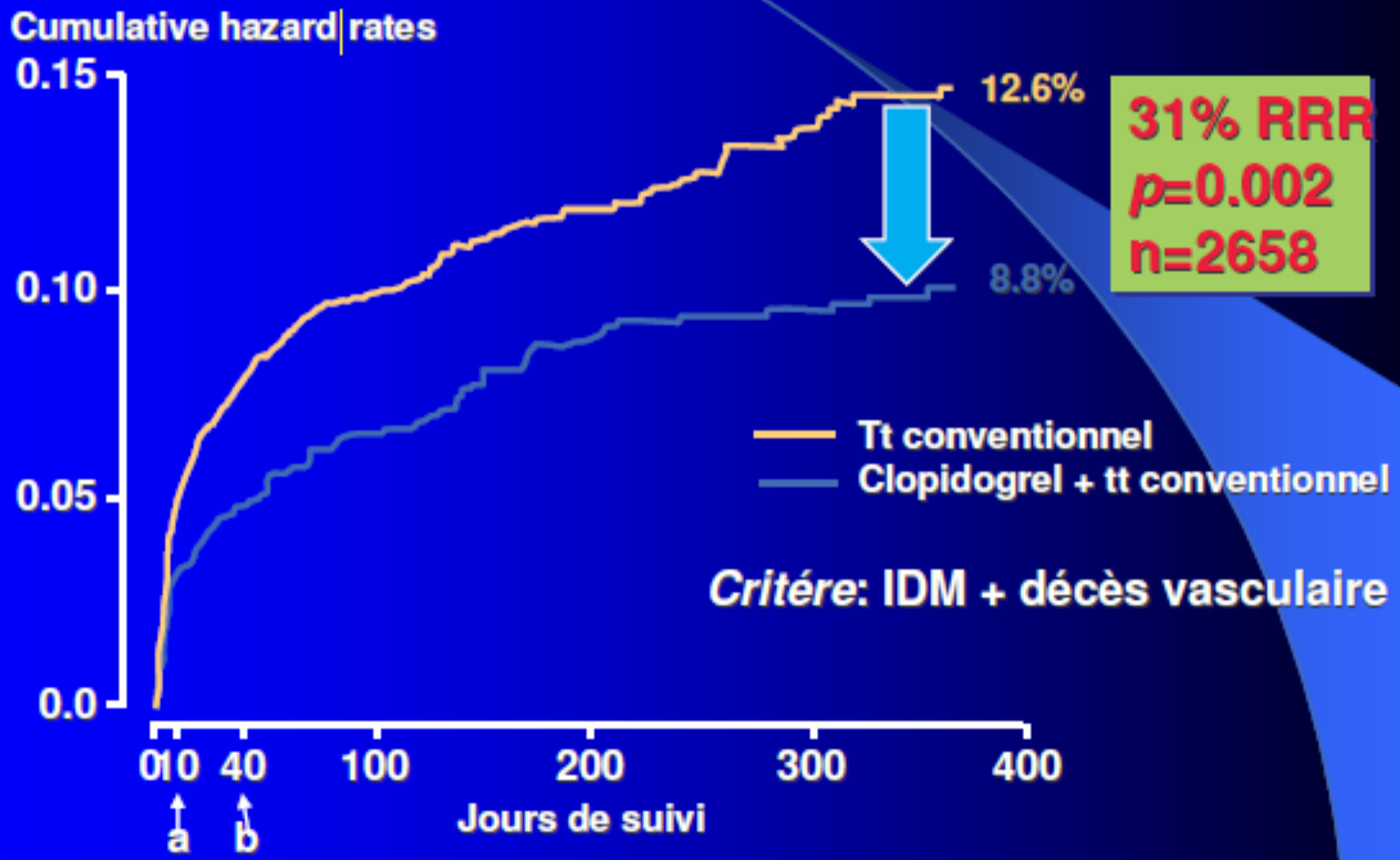


Figure 6 Death, myocardial infarction, and major bleeds at the end of study medication in four randomized trials of aspirin (filled bars) vs. control (open bars). NNT = number of patients who needed to be treated to avoid one event.

PCI-CURE

Résultats à long terme de la randomisation à la fin du suivi



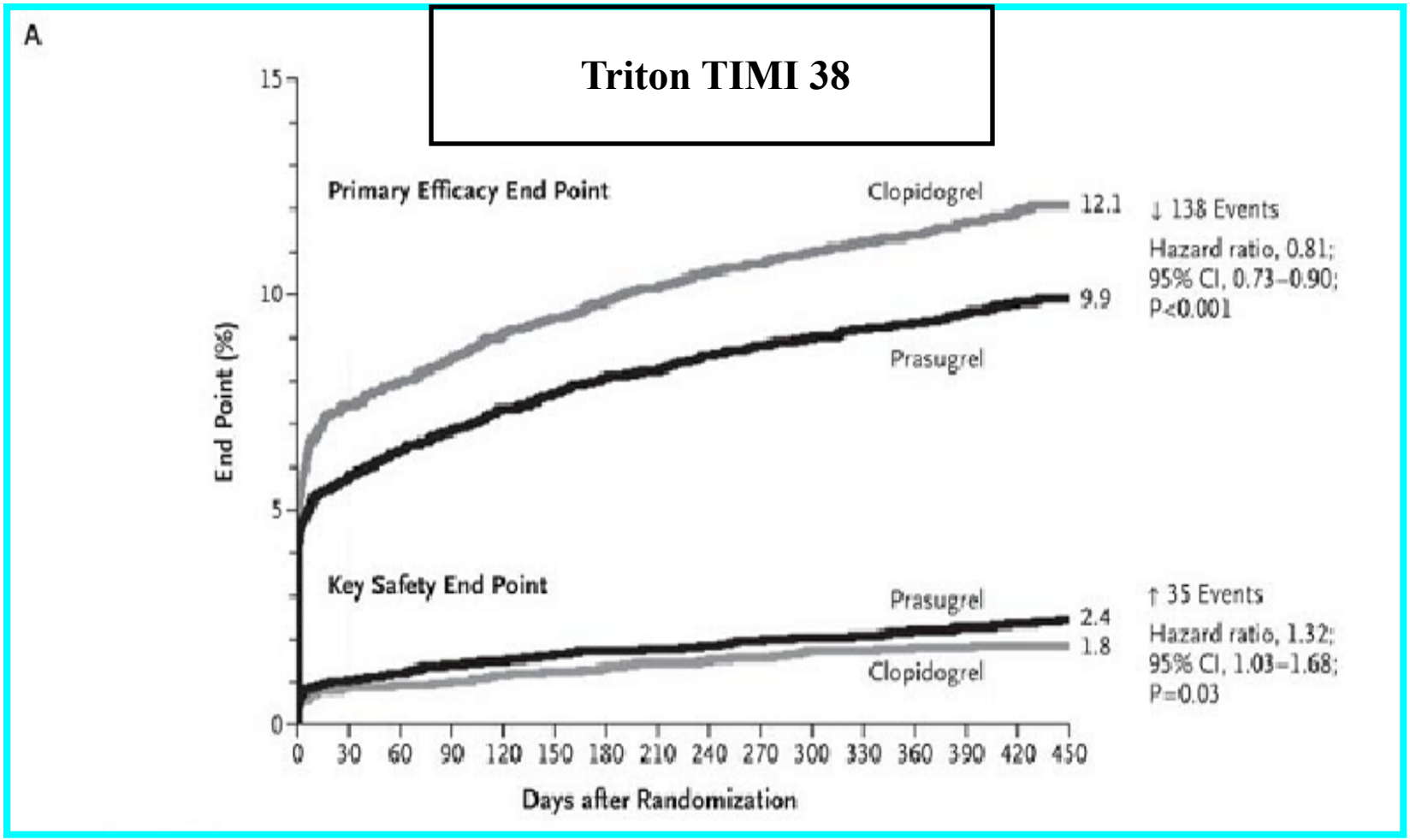
a = délais médian randomisation /ACP (10 jours)
b = 30 jours aprés ACP

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Prasugrel (N=6813)	Clopidogrel (N=6795)
Unstable angina or NSTEMI (%)	74	74
STEMI (%)	26	26
Age		
Median (yr)	61	61
25th percentile, 75th percentile (yr)	53, 69	53, 70
≥75 yr (%)	13	13
Female sex (%)	25	27
PCI	99	99
CABG	1	1
Stent	94	95
Bare-metal stent only	48	47
≥1 Drug-eluting stent	47	47
Multivessel PCI	14	14
Antithrombin use to support PCI (%)		
Heparin	66	65
LMWH	9	8
Bivalirudin	3	3
Other or multiple therapies	22	23
Glycoprotein IIb/IIIa–receptor antagonist use during index hospitalization (%)	54	55
Timing of study-drug administration (%)¶		
Before PCI	26	25
During PCI	73	74
After PCI	1	1
Pharmacotherapy during index hospitalization (%)		
ACE inhibitor or ARB	76	75
Beta-blocker	88	88
Statin	92	92
Calcium-channel blocker	18	17
Aspirin	99	99

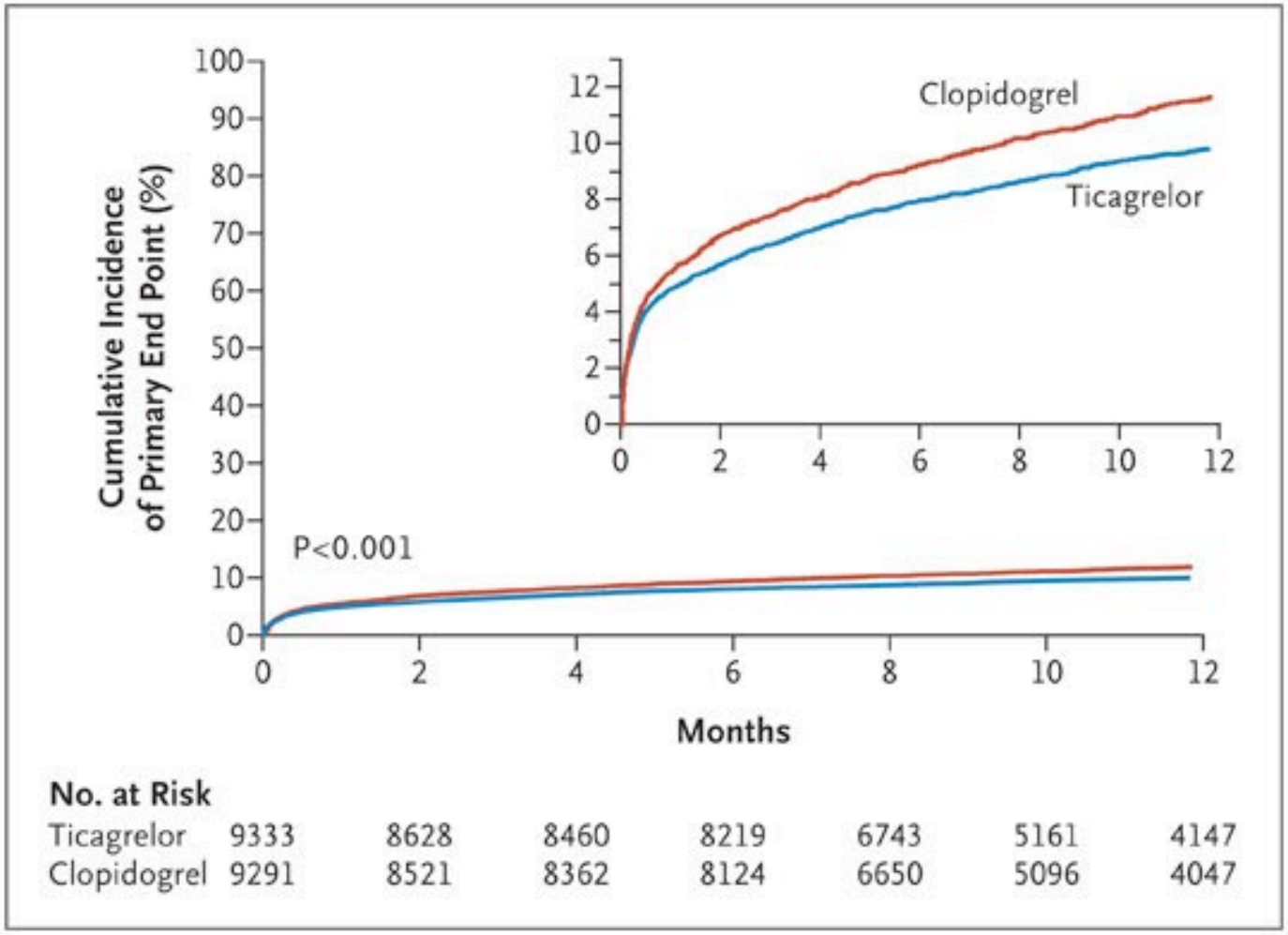
Triton TIMI 38

Triton TIMI 38



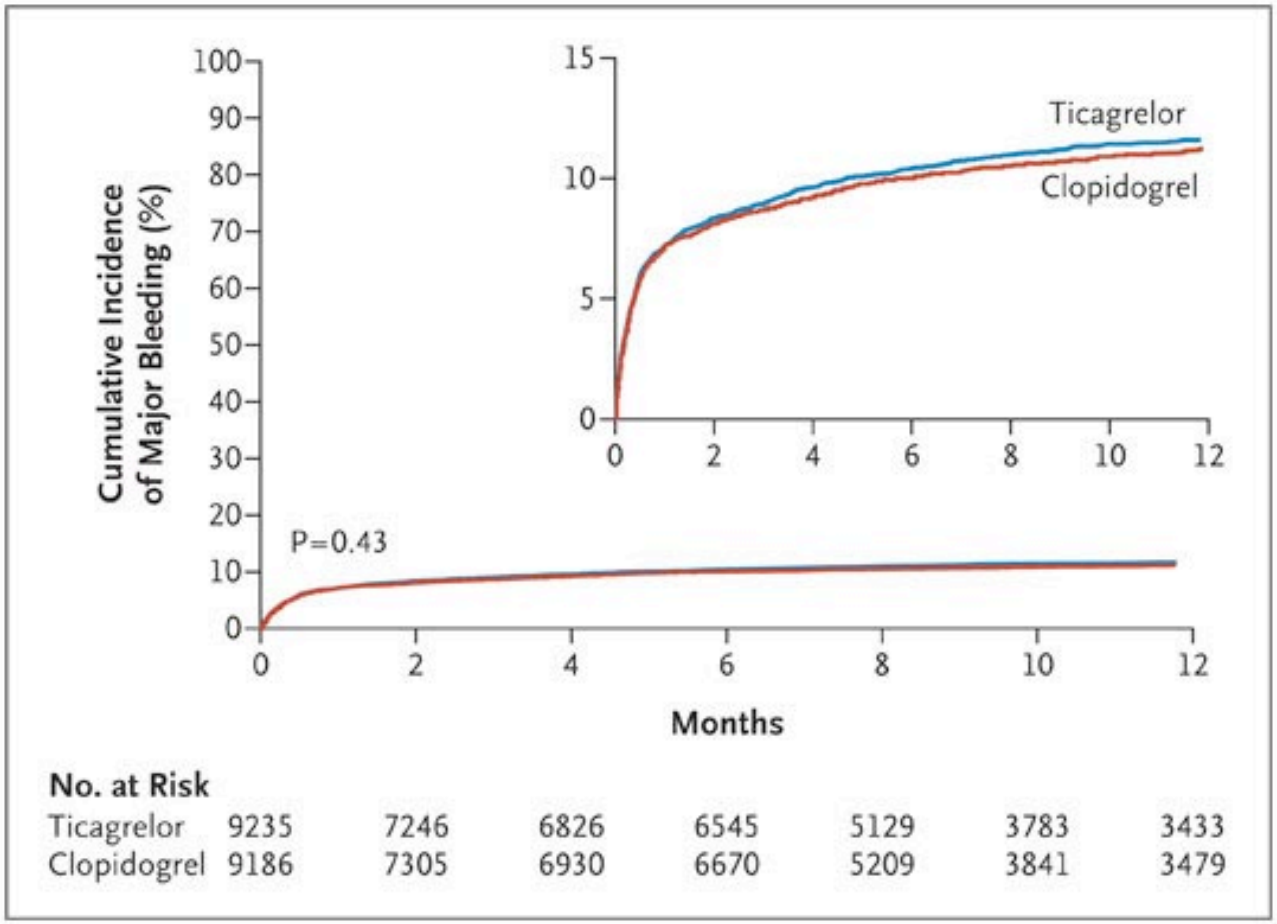
Plato:

Critère primaire



Plato:

Saignements



Y a t-il encore une place pour les antiGp2b3a?

2007

Recommendations for glycoprotein IIbIIIa inhibitors (Table 6)

- In patients at intermediate to high risk, particularly patients with elevated troponins, ST-depression, or diabetes, either eptifibatide or tirofiban for initial early treatment is recommended in addition to oral antiplatelet agents (IIa-A).
- The choice of combination of antiplatelet agents and anticoagulants should be made in relation to risk of ischaemic and bleeding events (I-B).
- Patients who receive initial treatment with eptifibatide or tirofiban prior to angiography should be maintained on the same drug during and after PCI (IIa-B).
- In high-risk patients not pre-treated with GP IIb/IIIa inhibitors and proceeding to PCI, abciximab is recommended immediately following angiography (I-A). The use of eptifibatide or tirofiban in this setting is less well established (IIa-B).
- GP IIb/IIIa inhibitors must be combined with an anticoagulant (I-A).
- Bivalirudin may be used as an alternative to GP IIb/IIIa inhibitors plus UFH/LMWH (IIa-B).

Recommandations II -A

Recommandations I-A

Recommandations IIa-B

Recommandations
sur les traitements antiagrégants

NSTE-ACS			
Antiplatelet therapy			
	ASA	I	C
	Clopidogrel (with 600 mg loading dose as soon as possible)	I	C
	Clopidogrel (for 9–12 months after PCI)	I	B
	Prasugrel[d]	IIa	B
	Ticagrelor[d]	I	B
	+ GPIIb–IIIa antagonists (in patients with evidence of high intracoronary thrombus burden)		
	Abciximab (with DAPT)	I	B
	Tirofiban, Eptifibatide	IIa	B
	Upstream GPIIb–IIIa antagonists	III	B
Anticoagulation			
Very high-risk of ischaemia[e]	UFH (+GPIIb–IIIa antagonists) or	I	C
	Bivalirudin (monotherapy)	I	B
Medium-to-high-risk of ischaemia[e]	UFH	I	C
	Bivalirudin	I	B
	Fondaparinux	I	B
	Enoxaparin	IIa	B
Low-risk of ischaemia[e]	Fondaparinux	I	B
	Enoxaparin	IIa	B

Pas d'indications en amont de la salle pour les antiGPIIb-IIIa

Recommandations

sur les traitements anticoagulants

NSTE-ACS			
Antiplatelet therapy			
	ASA	I	C
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	Abciximab (with DAPT)	I	B
	Tirofiban, Eptifibatide	IIa	B
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Anticoagulation			
Very high-risk of ischaemia[e]	UFH (+GPIIb–IIIa antagonists) or	I	C
	Bivalirudin (monotherapy)	I	B
Medium-to-high-risk of ischaemia[e]	UFH	I	C
	Bivalirudin	I	B
	Fondaparinux	I	B
	Enoxaparin	IIa	B
Low-risk of ischaemia[e]	Fondaparinux	I	B
	Enoxaparin	IIa	B

Les anticoagulants

Recommendations for anticoagulation

- Anticoagulation is recommended for all patients in addition to antiplatelet therapy (I-A).
- Anticoagulation should be selected according to the risk of both ischaemic and bleeding events (I-B) (see also section 6.1 Bleeding complications, section 7.4 Chronic kidney disease, and section 7.5 Anaemia).
- Several anticoagulants are available, namely UFH, LMWH, fondaparinux, and bivalirudin. The choice depends on the initial strategy (see section 8 Management strategies: urgent invasive, early invasive, or conservative strategies) (I-B).

Traitements anticoagulants

- **<u>Si patient à très haut risque ischémique</u>** → stratégie invasive immédiate avec:

  – **HNF** IVD 60 UI/kg + IVSE jusqu'à l'angioplastie (I-C);

  Si haut risque de saignement préférer:

  – **Bivalirudine** en monothérapie: bolus 0.75 mg/kg + entretien 1.75 mg /kg/h (I-B)

Traitements anticoagulants

- **<u>Patient à haut risque ischémique ou intermédiaire</u>** → prise en charge différée (24-72h):

    - **HNF** IVD 60 UI/kg + IVSE jusqu'à l'angioplastie (I-C);
    - **Enoxaparine**: 1 mg/kg 2*/j, (0.75 mg/kg si âge > 75) (IIA-B);
    - **Fondaparinux** 2.5 mg sc /j (I-B);
    - **Bivalirudine** 0.1 mg/kg IV bolus, puis perfusion 0.25 mg/kg/h (I-B);

Traitements anticoagulants

- **<u>Pendant l'angioplastie</u>**:
  - Si HNF seule: ACT 250-350S
  - Si HNF + antiGP IIb-IIIa: ACT 200-250s
  - Si Enoxaparine:
    - Dernière injection entre 8-12h: bolus 0.3 mg/kg IV
    - Dernière injection > 12H, bolus 0.75 mg/kg IV
  - Si Bivalirudine: bolus additionnel 0.5 mg/kg et perfusion augmentée à 1.75 mg/kg/h
  - Si Fondaparinux: bolus HNF 50-100 UI/kg

HBPM versus HNF

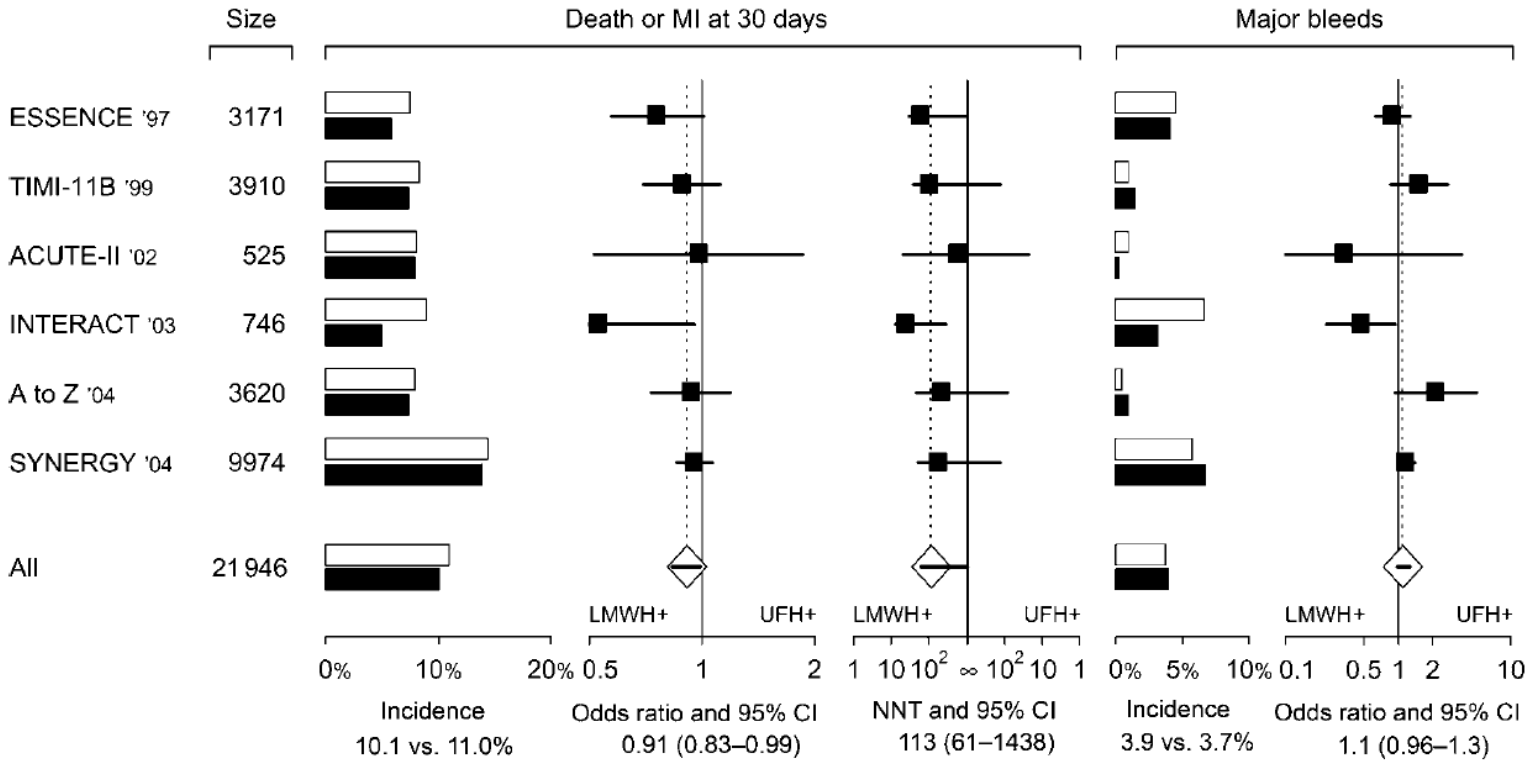
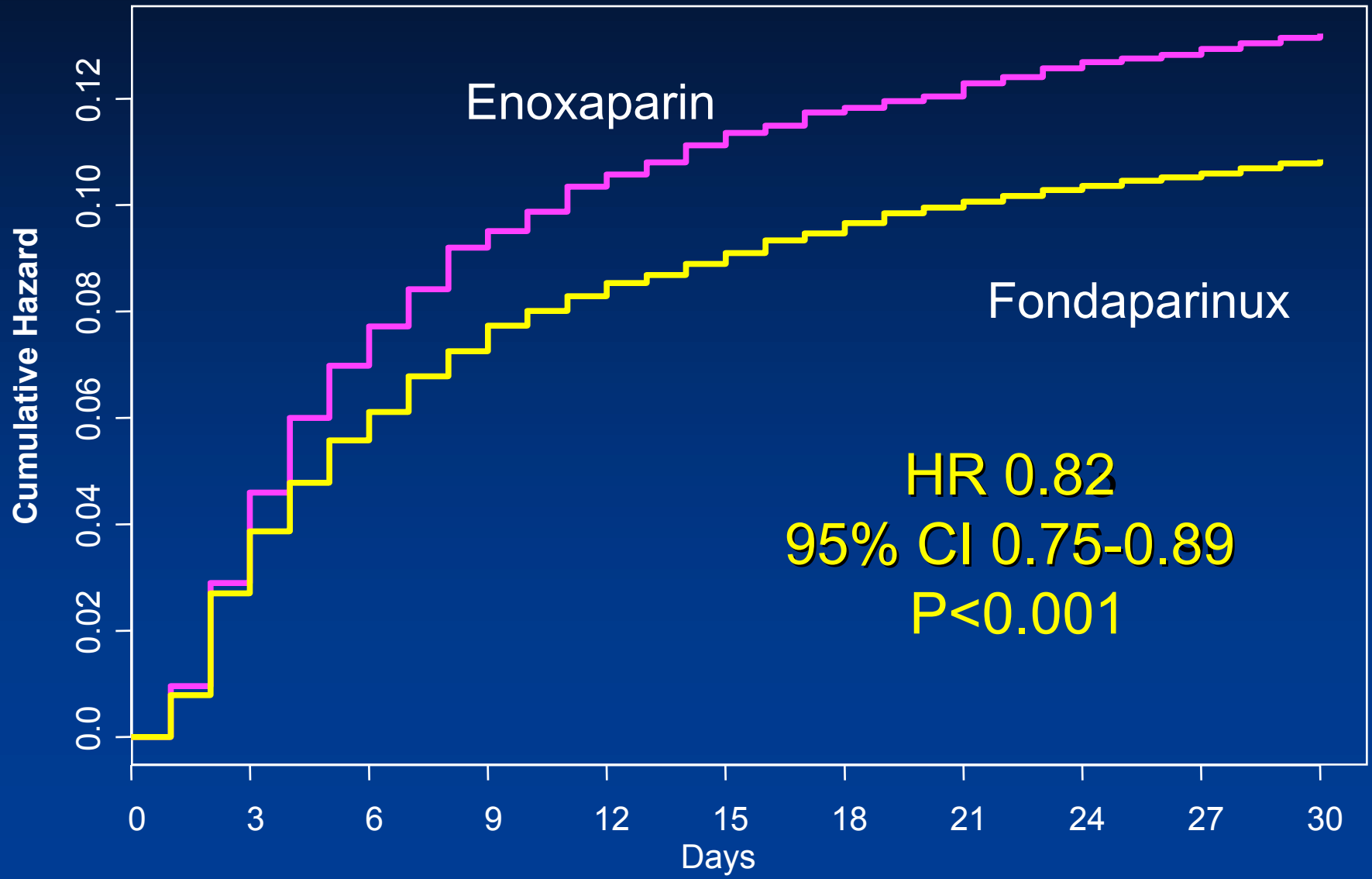
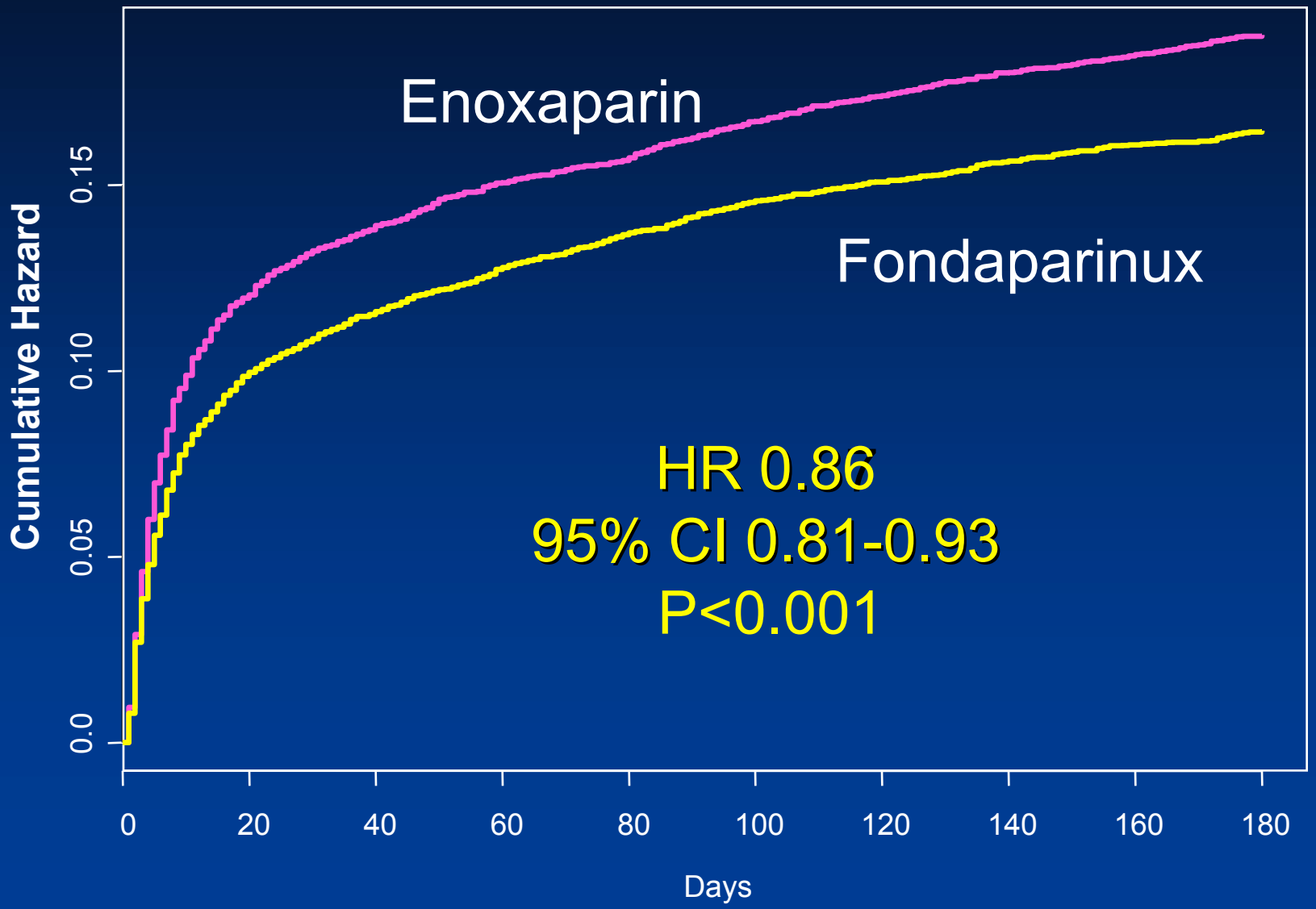


Figure 4 Death, myocardial infarction, and major bleeds at 30 days in randomized trials of enoxaparin (filled bars) vs. unfractionated heparin (open bars). NNT = number of patients who needed to be treated to avoid one event.

Death/MI/RI/Major Bleeds: Day 30



Death, MI, RI, Major Bleeding at 6 Months

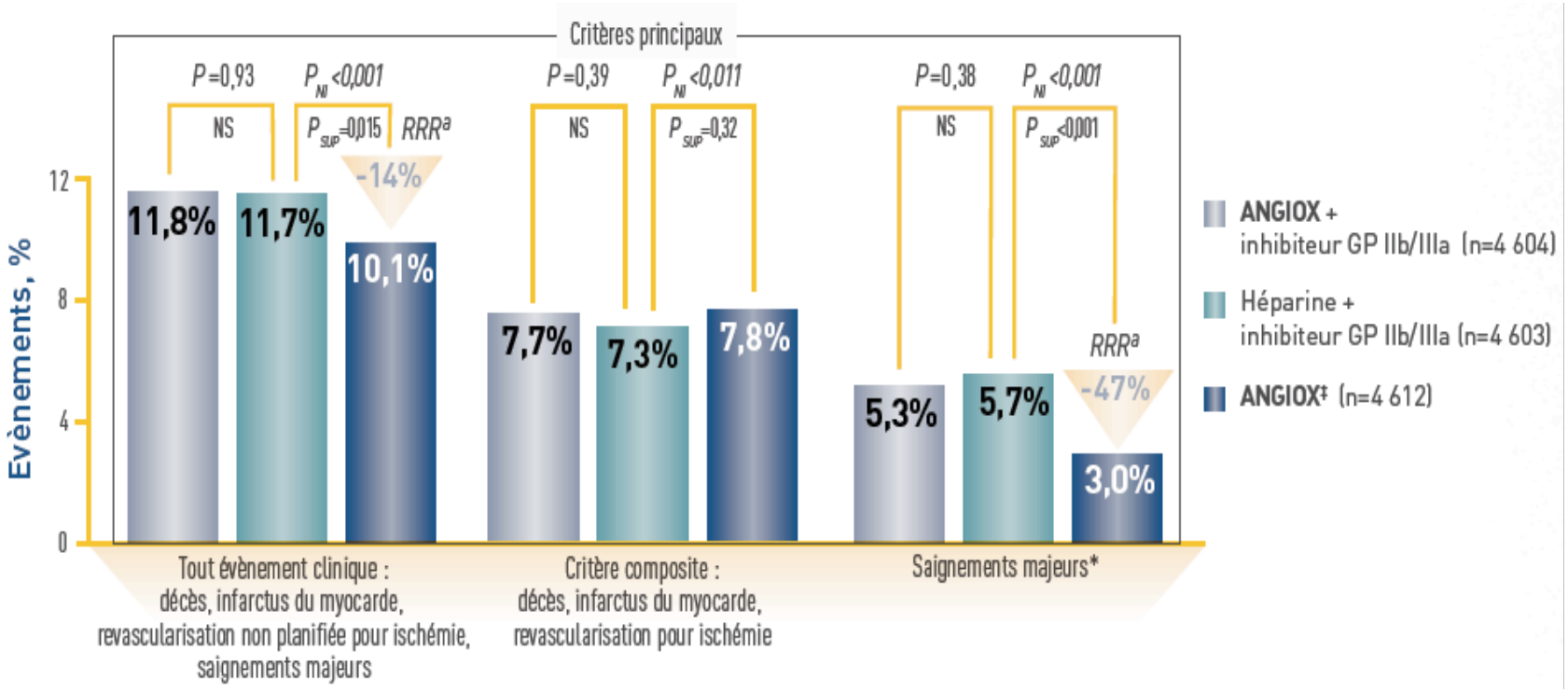


Acuity

ACUITY : principaux résultats de la bivalirudine seule vs HNF/HBPM + anti-IIb/IIIa

Critère	HNF/HBPM + anti-IIb/IIIa	Bivalirudine	RR (IC)	p non-supériorité	p non-infériorité
Critère composite ischémique (%)	7,3	7,8	1,08 (0,93-1,24)	0,32	0,01
Saignements majeurs (%)	5,7	3,0	0,53 (0,43-0,65)	< 0,001	< 0,001
Bénéfice clinique net (%)	11,7	10,1	0,86 (0,77-0,97)	0,015	< 0,001

Acuity:
Résultats du critère principal



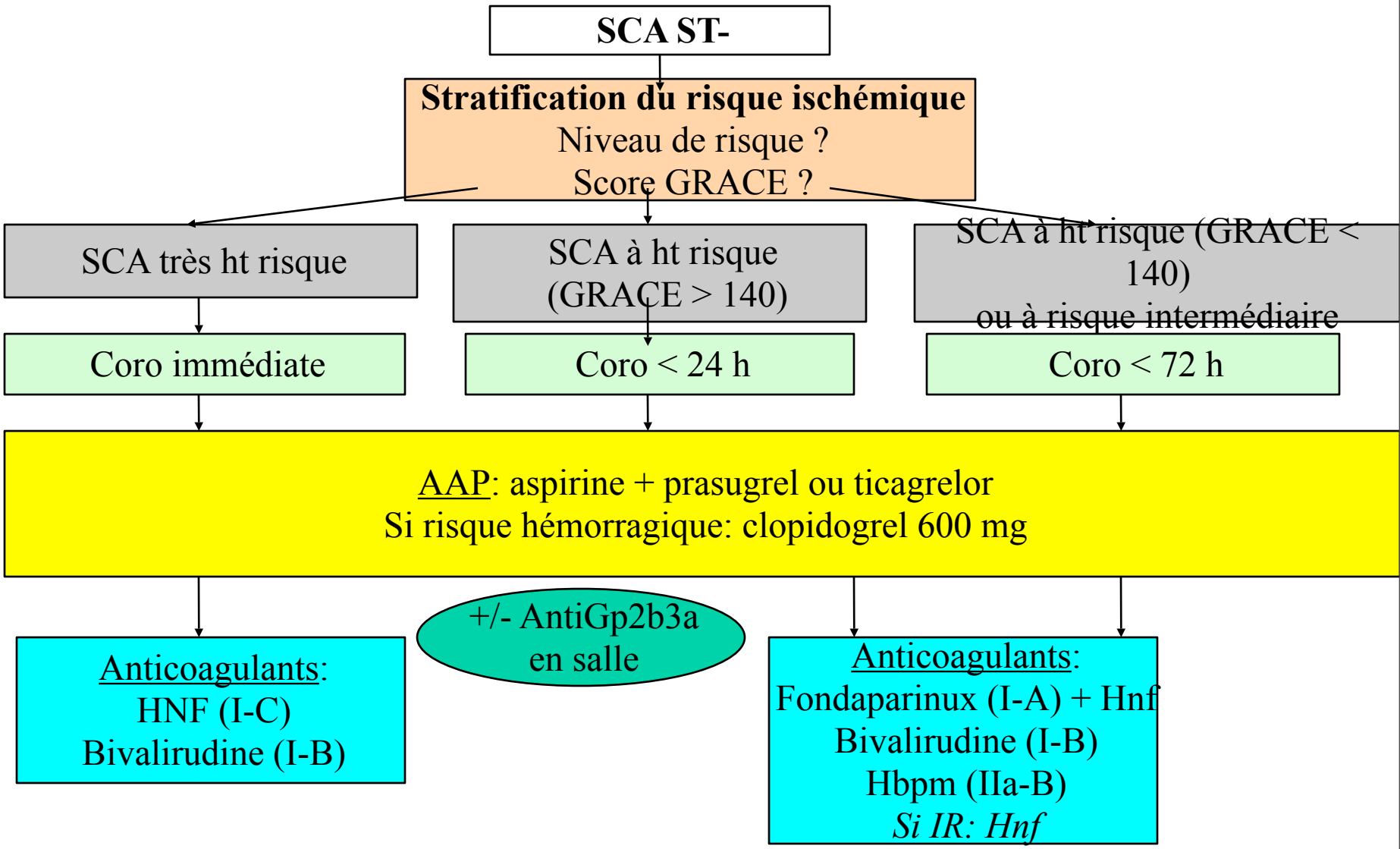
† 9.1% des patients sous ANGIOX ont reçu provisoirement GP IIb/IIIa

Saignements majeurs : défini dans ACUITY comme non-GABG intracrânien, rétropéritonéal ou saignement intra-occulaire ; saignement du point de ponction nécessitant une intervention ; hématome de ≥ 5 cm de diamètre ; réduction de la concentration d'hémoglobine de ≥ 4g/dl sans une source manifeste de saignement ; réduction de la concentration d'hémoglobine de ≥ 3g/dl avec une source manifeste de saignement ; ré-opération pour saignement ; utilisation d'un produit sanguin en transfusion

Stone GW et al. N Engl J Med. 2006;355:2203-2216.

en pratique,

- Privilégier la voie d'abord **radiale**:
  - Réduction de 60-70% des complications hémorragiques, (Triton, Mortal),
- Identifier les patients à **risque hémorragique** et éviter les surdosages: prudence chez les patients à plus haut risque: age > 75 ans, petit poids, insuffisance rénale, antécédents d'AVC ou saignements


SCA ST-
Stratification du risque ischémique
Niveau de risque ?
Score GRACE ?
SCA très ht risque
SCA à ht risque (GRACE > 140)
SCA à ht risque (GRACE < 140)
ou à risque intermédiaire
Coro immédiate
Coro < 24 h
Coro < 72 h
AAP: aspirine + prasugrel ou ticagrelor
Si risque hémorragique: clopidogrel 600 mg
+/- AntiGp2b3a
en salle
Anticoagulants:
HNF (I-C)
Bivalirudine (I-B)
Anticoagulants:
Fondaparinux (I-A) + Hnf
Bivalirudine (I-B)
Hbpm (IIa-B)
Si IR: Hnf