Collège National des Cardiologues des Hôpitaux

Le patient à haut risque post SCA: l'évolutivité clinique est elle controlable?

Nicolas Delarche

CH F. Mitterrand, Pau

CNCH, le 24/11/2017
Symposium Astra Zeneca

Collège National des Cardiologues des Hôpitaux

DÉCLARATION DE RELATIONS PROFESSIONNELLES

Conférencier : Nicolas Delarche

☑Je déclare les liens d'intérêt potentiel suivants:

Consultant, expertises et recherche clinique:
Astra Zeneca, Bayer, Amgen, Sanofi, Pfizer, BMS, Novartis

EUROPA ORGANISATION
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SCA à haut risque
définition du risque résiduel

- Risque résiduel de cholestérol
  - LDL-c élevé
  - CRPus basse
- Risque résiduel d'inflammation
  - LDL-c bas
  - CRPus élevée
- **<u>Risque résiduel thrombotique</u>**

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SCA à haut risque
définition du risque résiduel

- **Les MACCE**:
  - 5% à un an, (décès, infarctus, AVC)
    - Décès cardiovasculaires (3% / an)
    - Récidives ischémiques, (SCA et revascularisation même territoire ou non)
    - Évolution de l'athérome sur d'autres territoires, (AVC, AOMI)
    - **<u>Malgré un traitement adapté</u>**

- **2 périodes**:
  - **< 12 mois**: courbe non linéaire décroissante d'évènements en rapport avec l'épisode initial
  - **> 12 mois**: courbe linéaire d'évènements non nuls

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SCA à haut risque
définition du risque résiduel

- Au niveau coronaire:
  - Risques sur le vaisseau cible du SCA
    - Resténose intrastent (18% à 4 ans avec les stents actifs – polymère dégradable – dernière génération)
    - Progression de l'athérome à proximité;
  - Risques sur les vaisseaux non traités:
    - Aggravation de lésions coronaires initialement non critiques

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SCA à haut risque
le risque résiduel

- **Ce que nous avons appris des études:**
  - **OACIS**
  - **REACH**
  - **GRACE**
  - **APOLLO**
  - **PROTECT**
  - **PEGASUS TIMI 54**

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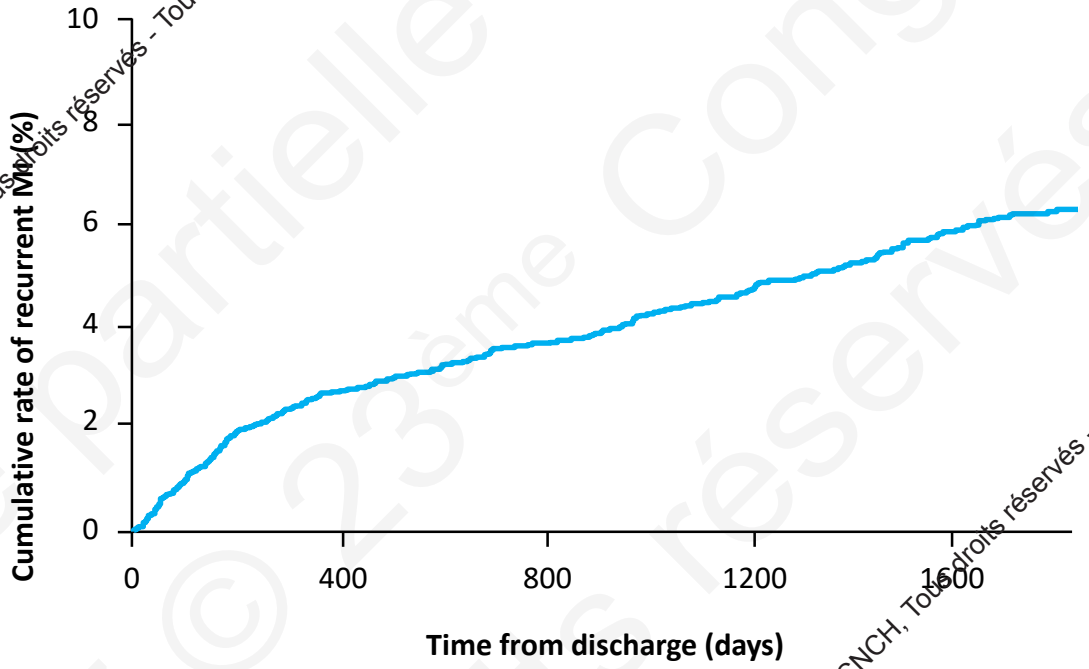
OACIS

The Highest Risk of Recurrent MI Occurs in the Initial Year Post-Discharge, but the Risk Is Continuous and Linear up to Year 5

- **OACIS Registry**: Observational study of **recurrent MI** in Japanese patients with acute MI with up to **5 years** of follow-up (n=7870)



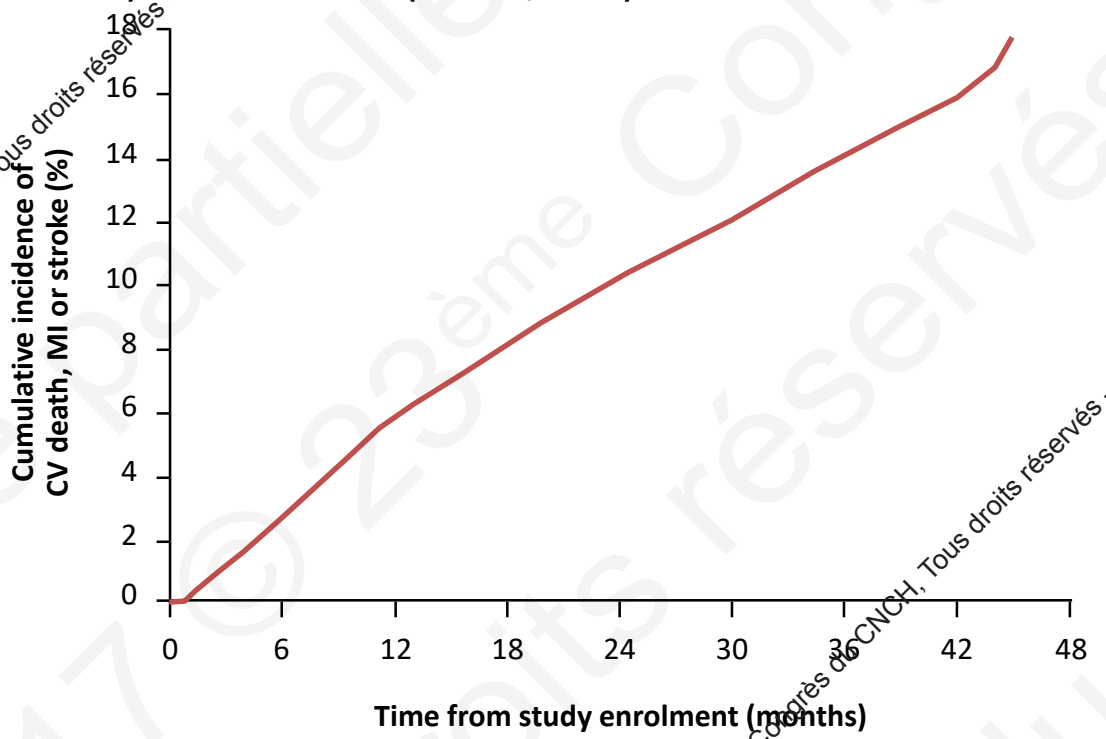
Risk for recurrent MI stays constant over a 5-year period; this is consistent with risk data across different registries and countries

MI, myocardial infarction; OACIS, Osaka Acute Coronary Insufficiency Study
Nakatani D *et al. Circulation* 2013;77:439–446

REACH

Prior MI Patients Both With and Without History of Ischaemic Events Have a Continuous and Linear Risk of **CV Death, MI, or Stroke for >3 Years**

- **REACH Registry***: CV risk in patients with a **history of ischaemic events** (MI or stroke) at baseline (n=21,890)



*A prospective, observational registry of outpatients ≥45 years of age with established history of CAD, CVD, PAD, or ≥3 atherosclerosis risk factors were followed up to 48 months

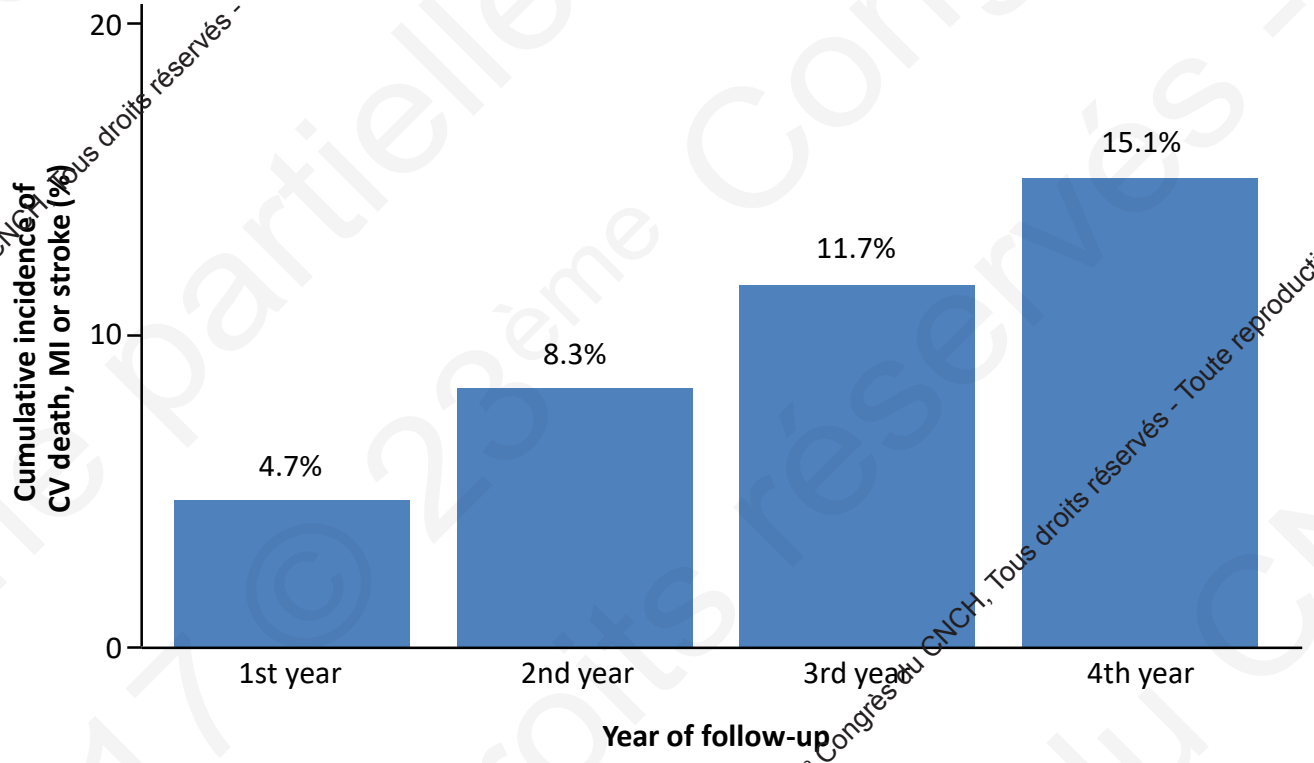
CAD, coronary artery disease; CV, cardiovascular; CVD, CV disease; MI, myocardial infarction; PAD, peripheral artery disease; REACH, REduction of Atherothrombosis for Continued Health

Bhatt DL *et al. JAMA* 2010;304:1350–1357

REACH

Prior MI Patients Both With and Without History of Ischaemic Events Have a Continuous and Linear Risk of CV Death, MI, or Stroke for >3 Years

- **REACH Registry**: **4-year** event rate in patients **with prior MI** and no history of stroke or TIA (n=32,307*)

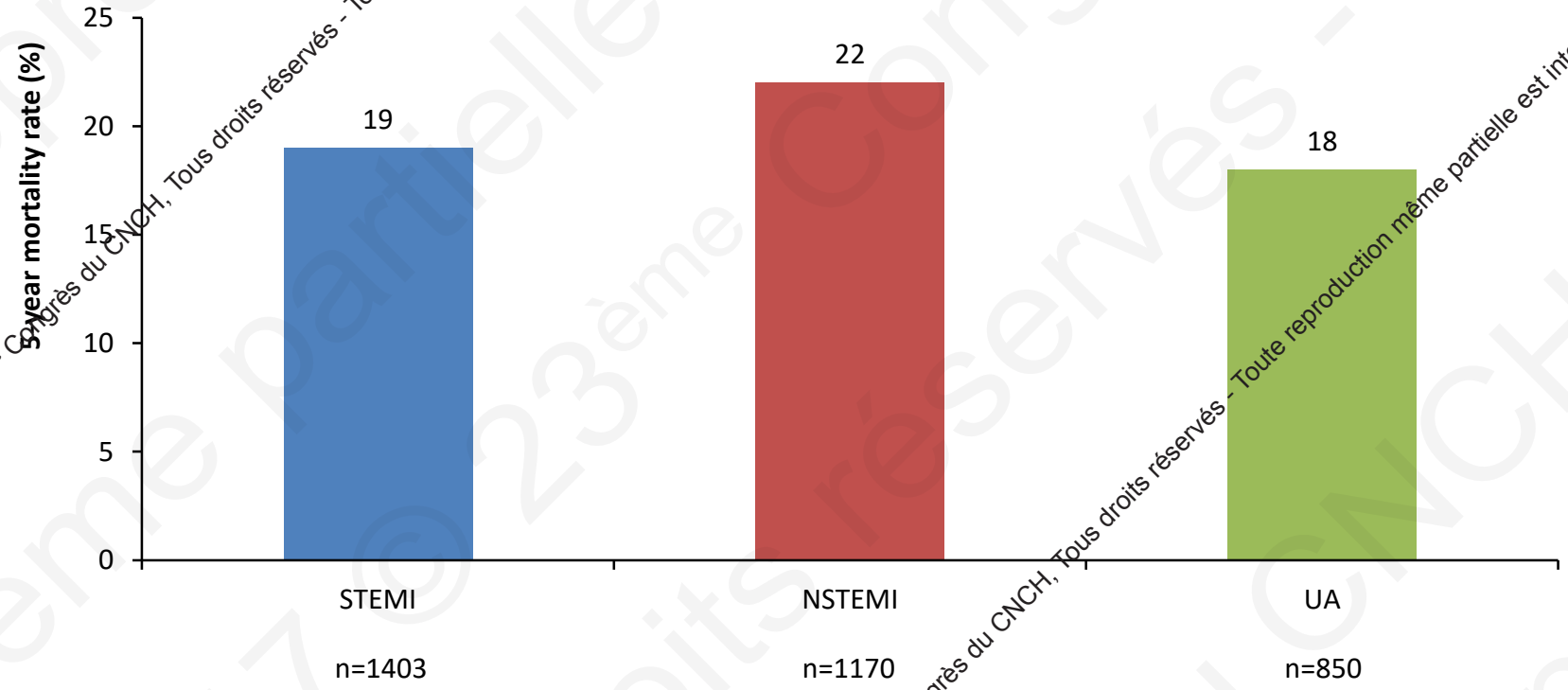


*Out of 65,531 initially enrolled in the study, 49.3% (n=32,307) were eligible for 4-year follow-up
CV, cardiovascular; MI, myocardial infarction; REACH, REduction of Atherothrombosis for Continued Health; TIA, transient ischemic attack
Abtan J *et al*. *Clin Cardiol* 2016;39:670–677

GRACE

1/5 Patients With ACS Will Have Died Within 5 Years of Their Index Event

- **GRACE Registry**: Long-term **5-year** prospective analysis of UK and Belgian patients with ACS (n>3000)



Post-discharge deaths occurred in 68%, 86% and 97% of STEMI, NSTEMI and UA patients, respectively

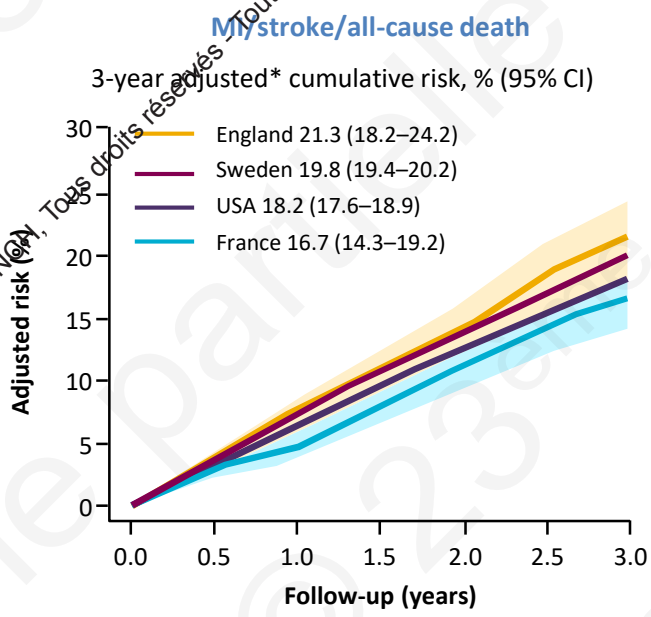
ACS, acute coronary syndromes; GRACE, Global Registry of Acute Coronary Events; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina

Fox KA *et al. Eur Heart J* 2010;31:2755–2764

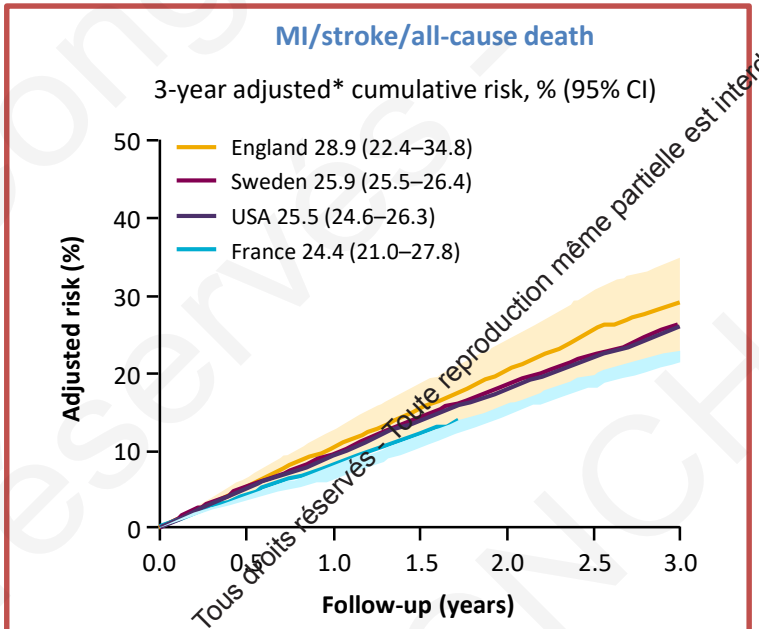
APOLLO

The "PEGASUS-Like" Cohort Showed an Elevated Cumulative Risk for **MI, Stroke, and All-Cause Death** Versus the Total Cohort

- APOLLO 4-country analysis* prospectively followed post-MI patients, event-free for 1 year, long-term over **3 years** (n>150,000)[1]



APOLLO 4-country total cohort (n>150,000)[1]



APOLLO cohort ≥65 years-old "PEGASUS-like" patients†[2]

Data are consistent across different registries and countries

*Adjusted for differences in study populations; †PEGASUS trial inclusion criteria included age ≥65 years-old as an additional risk factor
Shaded areas / figures in brackets [95%CI]
CI, confidence interval; MI, myocardial infarction; PEGASUS, Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin

1. Rapsomaniki E *et al.* ESC Oral presentation 2014; 2. Rapsomaniki E *et al. Eur Heart J Qual Care Clin Outcomes* 2016;2:172–183

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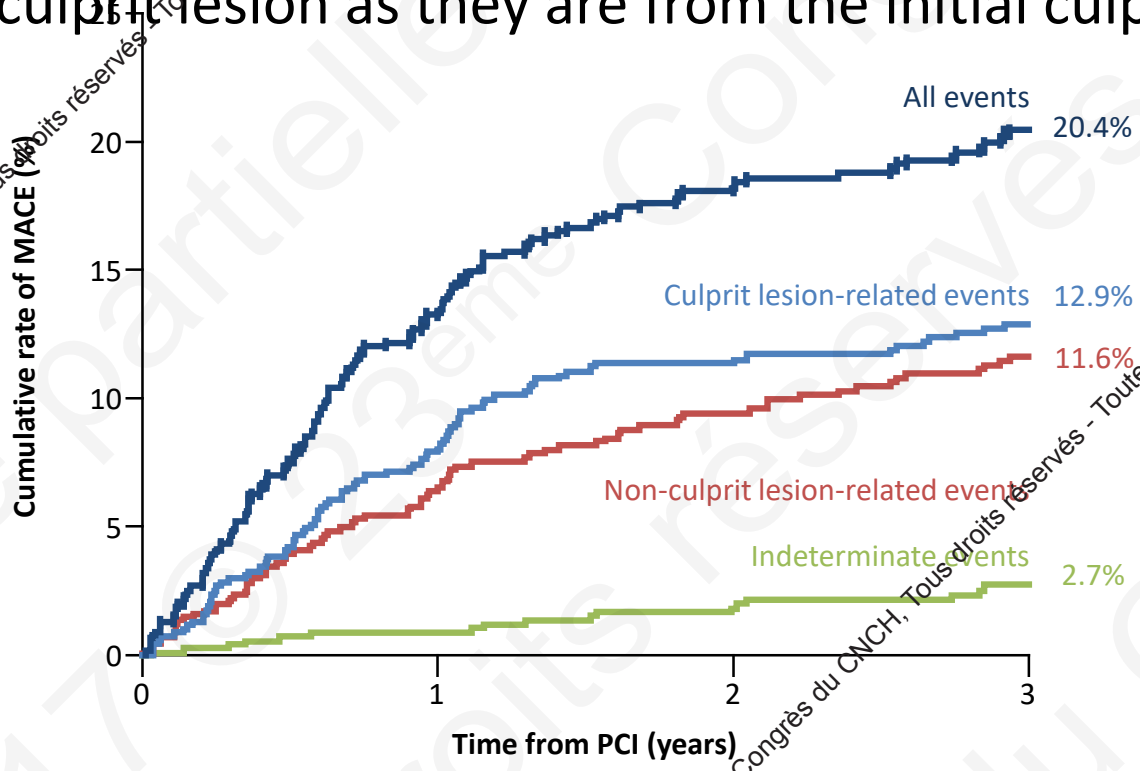
Anatomical Risk Factors: Non-Culprit Lesion Versus Initial Culprit Lesion

- Recurrent events in ACS patients are as likely to originate from a non-culprit lesion as they are from the initial culprit lesion



ACS, acute coronary syndromes; MACE, major adverse cardiac events; PCI, percutaneous coronary intervention; PROSPECT, Providing Regional Observations to Study Predictors of Events in the Coronary Tree

Stone GW *et al. N Engl J Med* 2011;364:226–235

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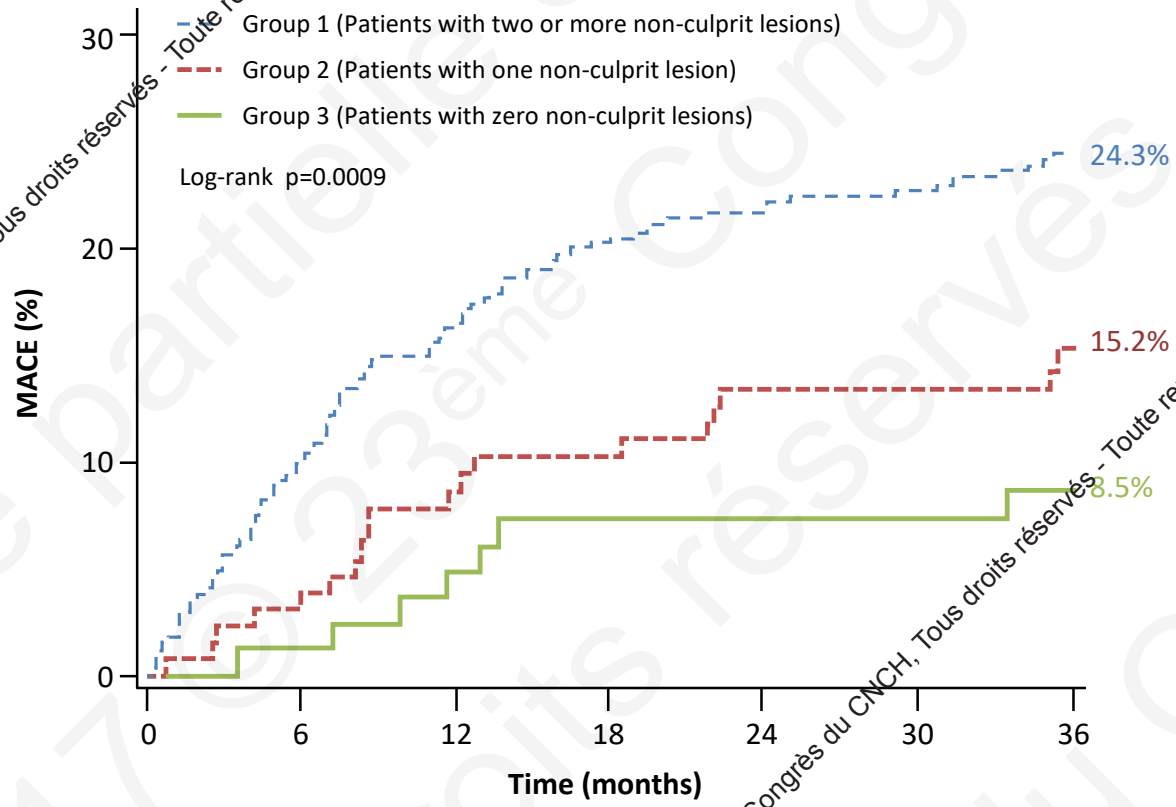
The Cumulative Incidence of MACE Increases Over Time With the Number of Non-Culprit Lesions in Patients With ACS



ACS, acute coronary syndromes; MACE, major adverse cardiac events; PROSPECT, Providing Regional Observations to Study Predictors of Events in the Coronary Tree
Brener SJ *et al. J Am Coll Cardiol Imag* 2012;5:S86–94

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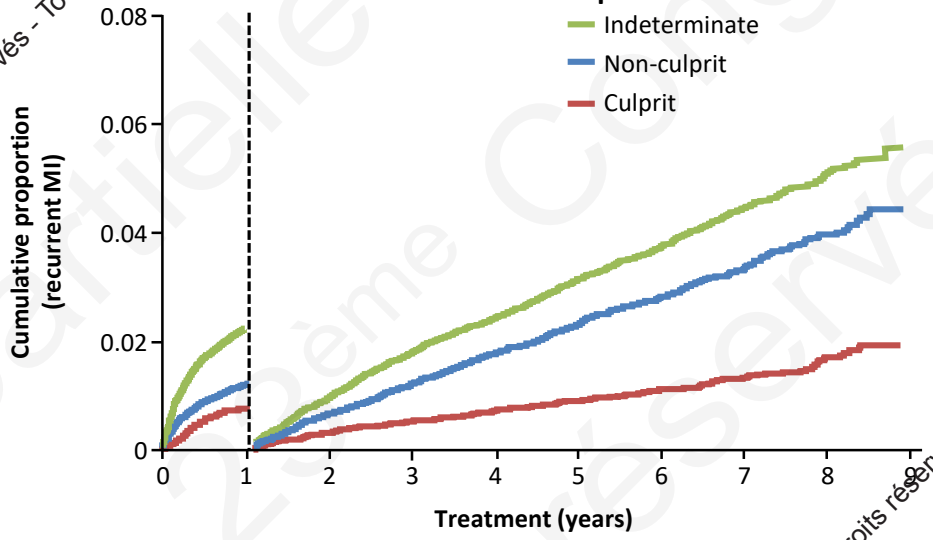
The Risk of Non-Culprit–Related **Recurrent MI** Is Twice That of Culprit-Related Recurrent MI

- SWEDEHEART (PRECLUDE): A prospective study with **8 years**' follow-up using data from SWEDEHEART and defined culprit lesion at index MI (n=41,789)



	Recurrent MI related to non-culprit (n=1193)	Recurrent MI related to culprit (n=597)	Indeterminate recurrent MI (n=1813)
Cumulative event probability at 8 years	0.06 (0.05–0.06)	0.03 (0.02–0.03)	0.07 (0.07–0.08)

CI, confidence interval; MI, myocardial infarction; PRECLUDE, Pattern of Repeat Cardiovascular Events During Follow-up After First Diagnosed Event-MI; SWEDEHEART, Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies

Varenhorst C *et al.* Oral presentation at AHA 2016

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SCA à haut risque
définition du risque résiduel

Objectifs prioritaires

- **<u>Identification des patients à haut risque</u>**
  - Assurer un suivi plus rapproché ?
  - Administrer une thérapeutique plus adaptée et agressive ?
    - **Prolongation de la DAPT**
    - Traitement hypocholestérolémiant plus intense

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SCA à haut risque
Facteurs influençant le risque résiduel

- **SCA – 1ère année**:
  - Complexité de la lésion coupable, (Yeh, JACC 2017, 18: 2213-2223)
  - Implantation d'un stent nu
  - Patient pluritronculaire
- **SCA - > 1ère année**:
  - NSTEMI
  - **Coronaropathie pluritronculaire**
  - **Patient âgé**
  - **Diabétique**
  - Antécédents cérébrovasculaires
  - Artériopathie périphérique
  - Antécédents de **cardiopathie ischémique** et d'insuffisance cardiaque
  - **Antécédents d'insuffisance rénale**

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SCA à haut risque: identification des patients à haut risque: quels examens pour quels patients? Une illusion…

- Détection de la **plaque vulnérable** (**écho-endo ou OCT**)
  - Corps nécrotique important
  - Chape fibreuse fine
  - Corps lipidique important
  - Dénudation de l'endothélium ou adhésion plaquettaire
  - Inflammation active
  - Étude **PROSPECT**:
    - Plaques à chape fine: risque accru de complication (*3,5)
    - Possibilité de stabilisation spontanée
    - Présence: valeur prédictive négative élevée, mais valeur prédictive positive faible < 25%
- Prévention de la **thrombose de stents**: multifactorielle
  - Précoce: défaut d'endothélialisation
  - Tardive: inflammation, néoprolifération, malapposition
  - Variables associées: arrêt prématuré de la DAPT, contexte de SCA, diabète, insuffisance rénale, dysfonction VG et critères anatomiques lésionnels (lésions type C, longueur > 20 mm et diamètre 3 mms, nombre de stents, diamètre luminal minimal en fin de procédure, dissection, thrombus résiduel ou malapposition)
- Détection de **l'ischémie résiduelle**:
  - place des explorations non invasives de stress
  - À quelle fréquence les répéter?

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SCA à haut risque:
identification des patients à haut risque
Les outils d'identification

- **Période instable**, < 12 mois (décès, infarctus, thrombose de stent)
  - Score **GRACE**, (prédiction du risque de décès)
  - Score **CRUSADE**, (risque hémorragique)
  - Score **PRECISE-DAPT**

- **Période stable**, > 12 mois
  - Score **DAPT**: (intégration des risques ischémiques et hémorragiques)
  - Score **SYNTAX** (evaluation de la complexité et diffusion des lésions coronaires initiales)
  - **Score angiographique** (3 vx, 2 stents /bif, cto, lg stent > 60 mm)
  - **Score calcique** coronaire (> 400: risque *3)
  - Atteinte artérielle périphérique (*2,5 le risque de survenue d'un évènement ischémique)
  - **Critères PEGASUS** ++

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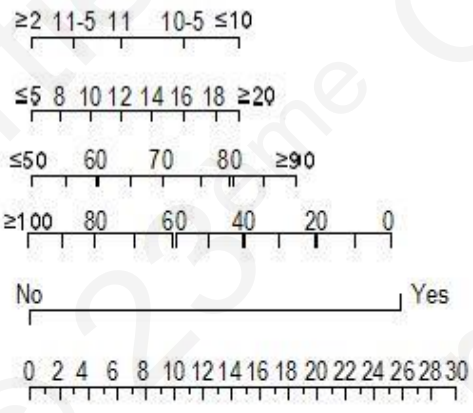
Risk scores validated for dual antiplatelet therapy duration decision-making

ESC European Society of Cardiology

	PRECISE-DAPT score	DAPT score
Time of use	At the time of coronary stenting	After 12 months of uneventful DAPT
DAPT duration strategies assessed	Short DAPT (3–6 months) vs. Standard/long DAPT (12–24 months)	Standard DAPT (12 months) vs. Long DAPT (30 months)
Score calculation		Age ≥75 −2 pt 65 to <75 −1 pt <65 0 pt Cigarette smoking +1 pt Diabetes mellitus +1 pt MI at presentation +1 pt Prior PCI or prior MI +1 pt Paclitaxel-eluting stent +1 pt Stent diameter <3 mm +1 pt CHF or LVEF <30% +2 pt Vein graft stent +2 pt
Score range	0 to 100 points	−2 to 10 points
Decision making cut-off suggested	Score ≥25 → Short DAPT Score <25 → Standard/long DAPT	Score ≥2 → Long DAPT Score <2 → Standard DAPT
Calculator	www.precisedaptscore.com	www.daptstudy.org

www.escardio.org/guidelines

2017 ESC Focused Update on DAPT in Coronary Artery Disease, developed in collaboration with EACTS (European Heart Journal 2017 - doi:10.1093/eurheartj/ehx419)

Prise en compte du risque hémorragique (>=25 ou <=2)

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Objectifs de la DAPT prolongée

- En termes d'ischémie: Réduction:
  - De survenue de nouveaux évènements ischémiques
  - Du risque de thromboses de stents
  - De la mortalité cardiovasculaire

- Pas d'augmentation:
  - Des hémorragies
  - De la mortalité non cardiovasculaire

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Données de vraie vie: prolongation de la DAPT

- Registre FAST-MI:
  - 75% des patients poursuivent la DAPT à un an et 43% à 2 ans

- Registre CRAC
  - > 50% des patients poursuivent la DAPT au-delà d'un an

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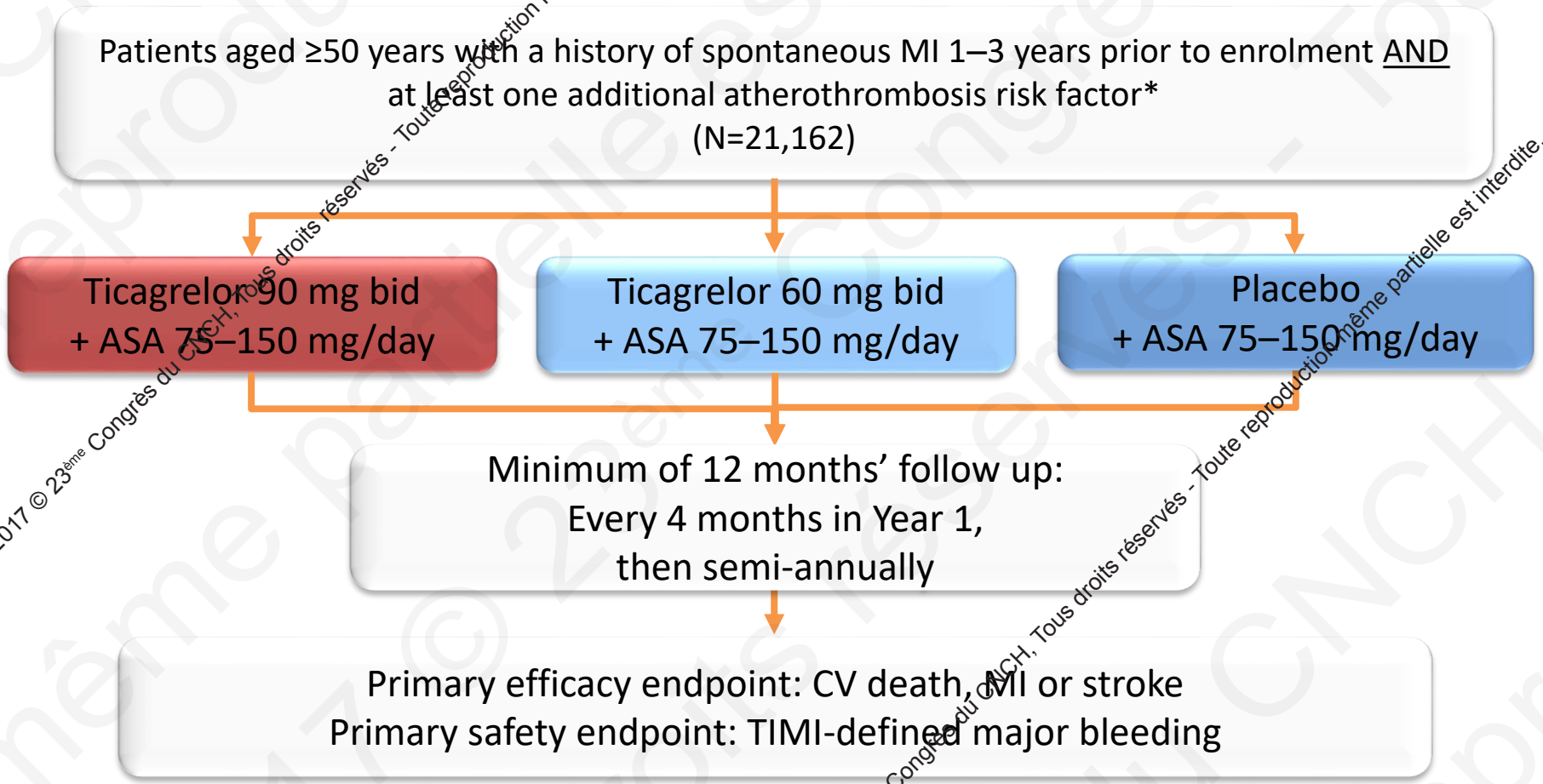
la DAPT prolongée
Les études

Etude	n	%sca	Effet isch.	Effets saignts
DES LATE 2010	2117	60%	12m = >12m	Pas de diff
EXCELLENT 2012	1443	50%	6m = 12m	Pas de diff
PRODIGY 2012	2013	75%	6m = 24m	Plus de saigmts
RESET 2012	2117	55%	3m = 12m	Pas de diff
OPTIMIZE 2013	3119	30%	3m = 12m	Plus de saigmts
ARTIC 2013	1259	25%	12m = >12m	Plus de saigmts
ISAR SAFE 2014	4005	40%	6m = 12m	Plus de saigmts
ITALIC 2014	2031	25%	6m = 24m	Pas de diff
DAPT 2014	9961	26%	30m > 12m	Plus de saigmts
PEGASUS 2015	21162	100%	33m > 12m	Plus de saigmts

PEGASUS-TIMI 54: Study Design



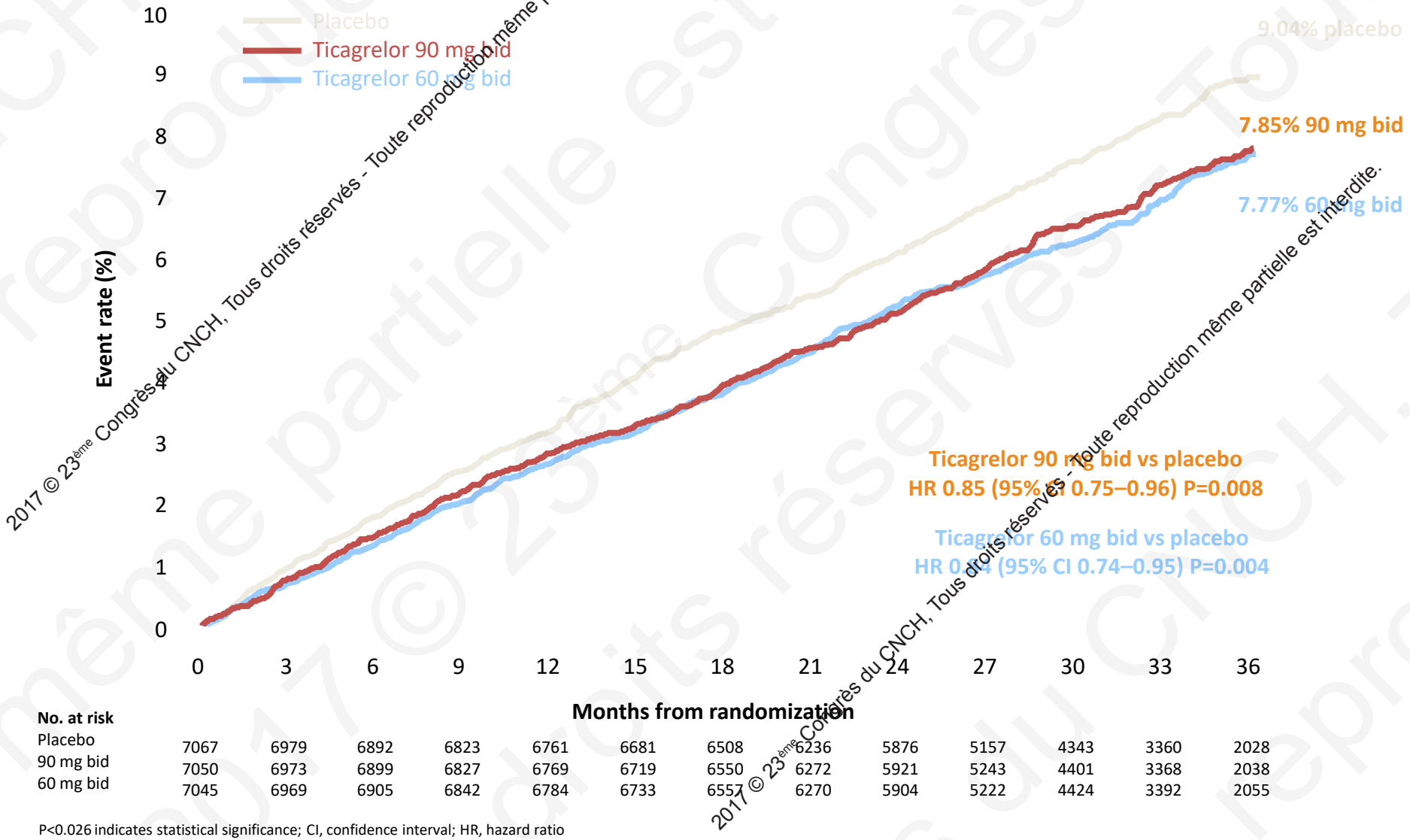
Bonaca MP *et al*. *N Engl J Med* 2015;372:1791–1800

PEGASUS-TIMI 54: Inclusion Criteria

- Age ≥50 years old
- History of a spontaneous MI 1–3 years prior to enrolment and one additional high-risk feature
  - Age ≥65 years old
  - Diabetes mellitus requiring medication
  - A second prior spontaneous MI
  - Angiographic evidence of multivessel CAD
  - Chronic, non-end-stage renal dysfunction (CrCl <60 mL/min)
- Prescribed and tolerating ASA at the time of enrolment

Bonaca MP *et al*. *N Engl J Med* 2015;372:1791–1800

PEGASUS-TIMI 54: Primary Endpoint

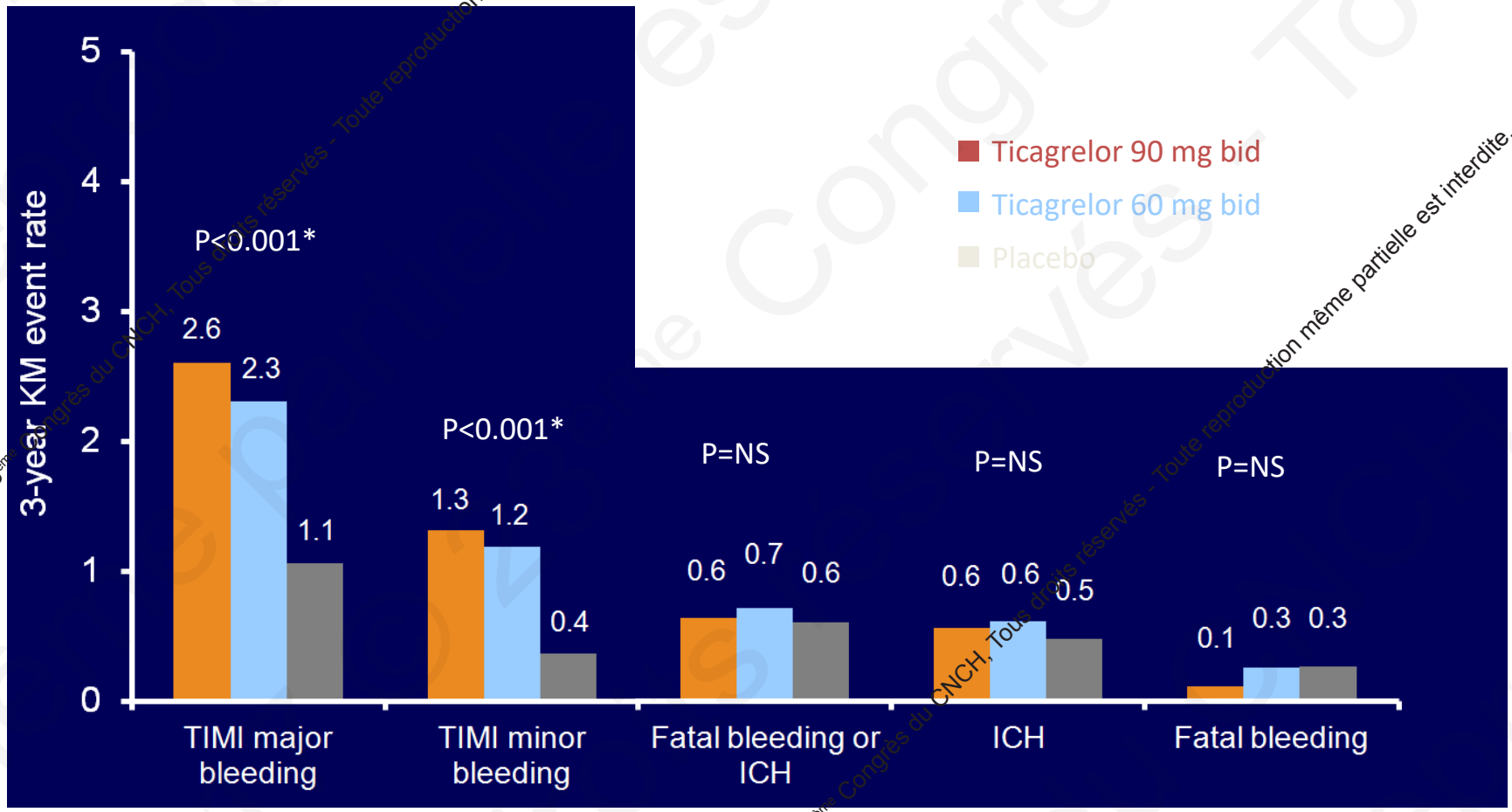


No. at risk													
Placebo	7067	6979	6892	6823	6761	6681	6508	6236	5876	5157	4343	3360	2028
90 mg bid	7050	6973	6899	6827	6769	6719	6550	6272	5921	5243	4401	3368	2038
60 mg bid	7045	6969	6905	6842	6784	6733	6557	6270	5904	5222	4424	3392	2055

P<0.026 indicates statistical significance; CI, confidence interval; HR, hazard ratio

Bonaca MP *et al. N Engl J Med* 2015;372:1791–1800

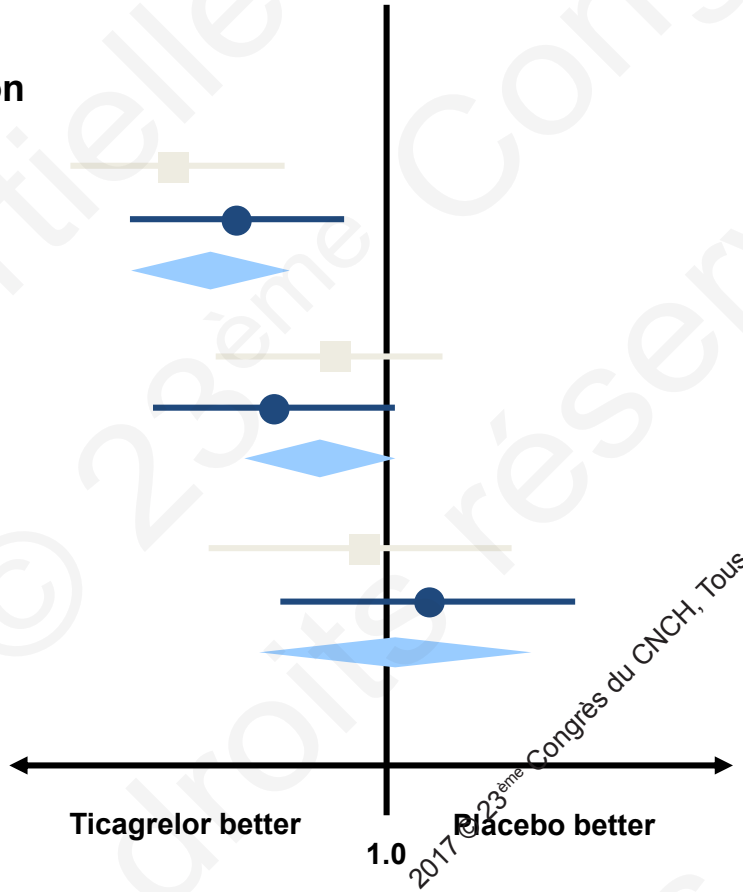
PEGASUS-TIMI 54: Bleeding



Indicates nominal P value
Rates are presented as 3-year Kaplan-Meier estimates
ICH, intracranial bleeding
Bonaca MP *et al. N Engl J Med* 2015;372:1791–1800

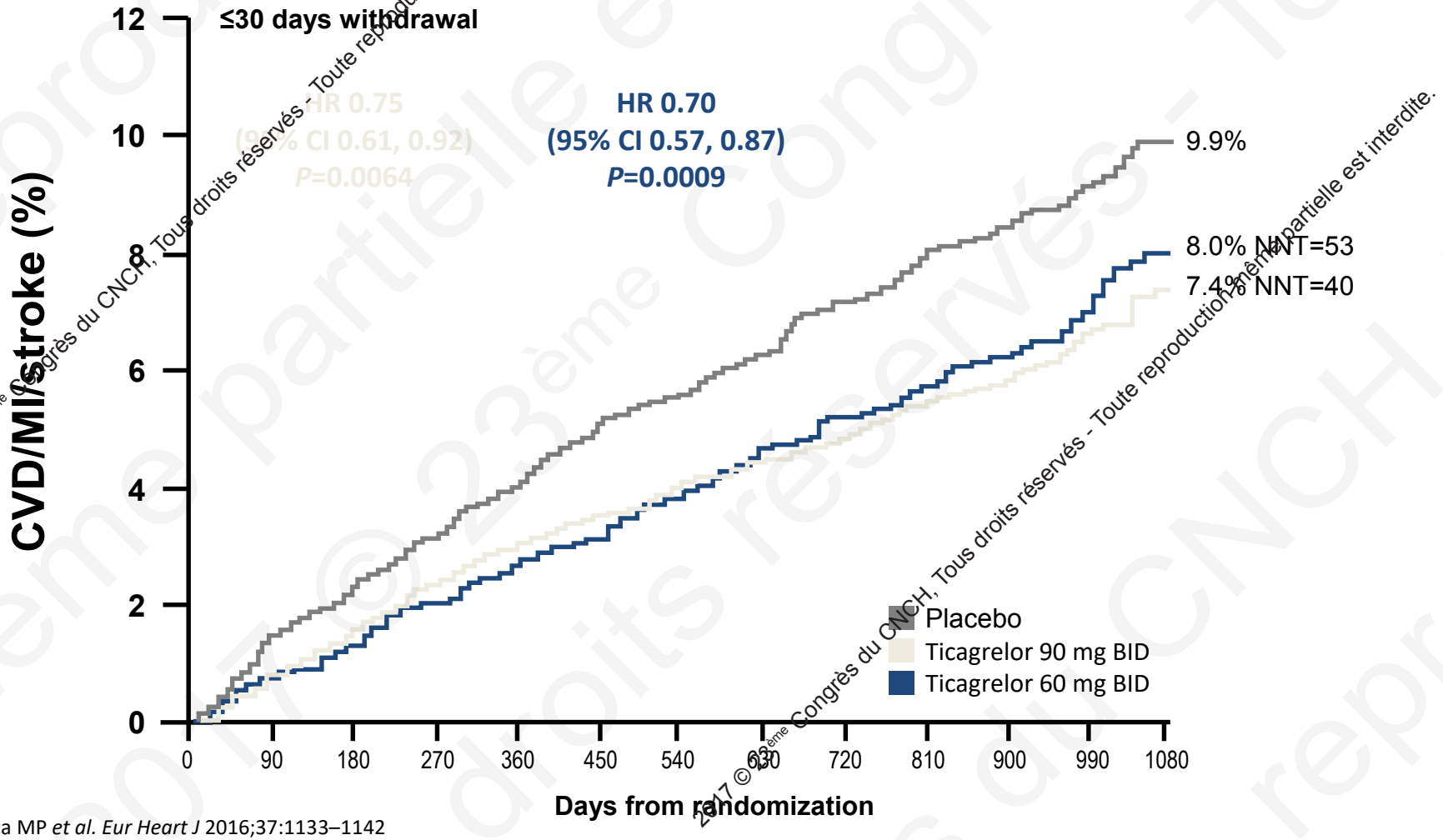
Efficacy of ticagrelor in reducing risk of atherothrombotic events declines with increasing duration of $P2Y_{12}$ inhibitor withdrawal

The greatest benefit was seen in patients who had discontinued $P2Y_{12}$ inhibition within 30 days, and the magnitude of this benefit was similar regardless whether the patient's qualifying MI was <2 years or ≥2 years prior to randomization



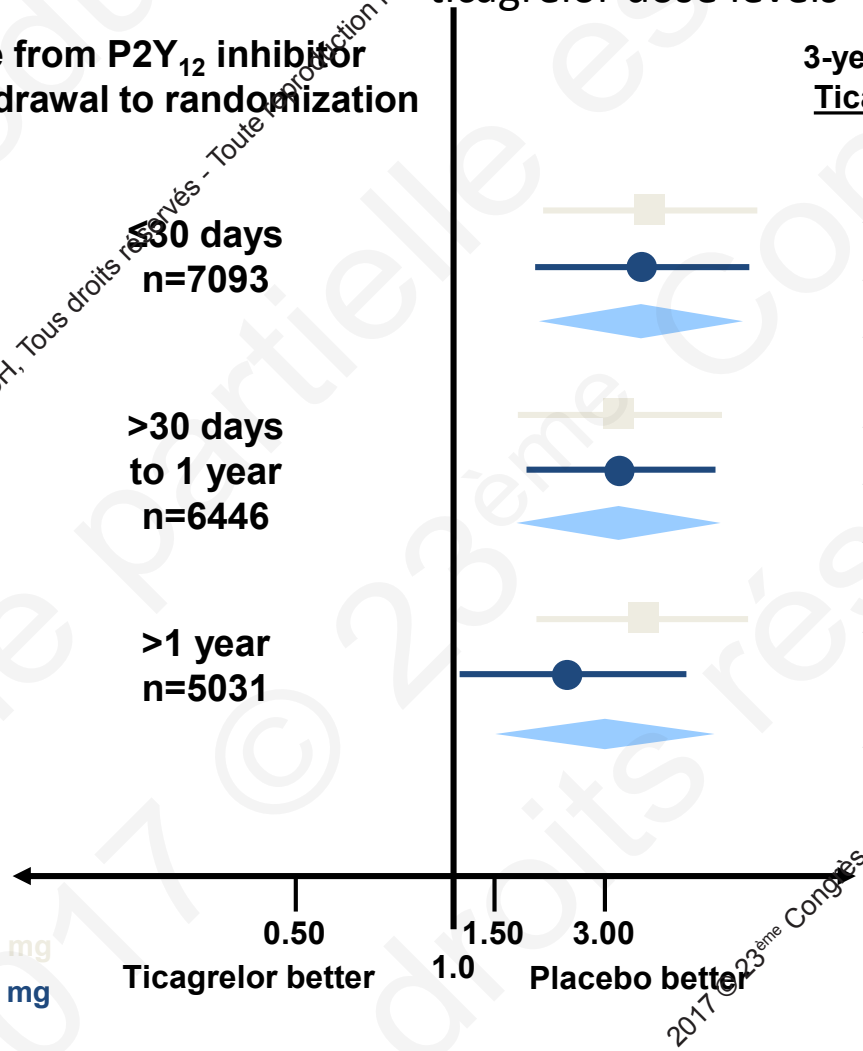
Bonaca MP *et al. Eur Heart J* 2016;37:1133–1142

The greatest benefit with ticagrelor was seen in patients who had discontinued $P2Y_{12}$ inhibition within 30 days of randomization

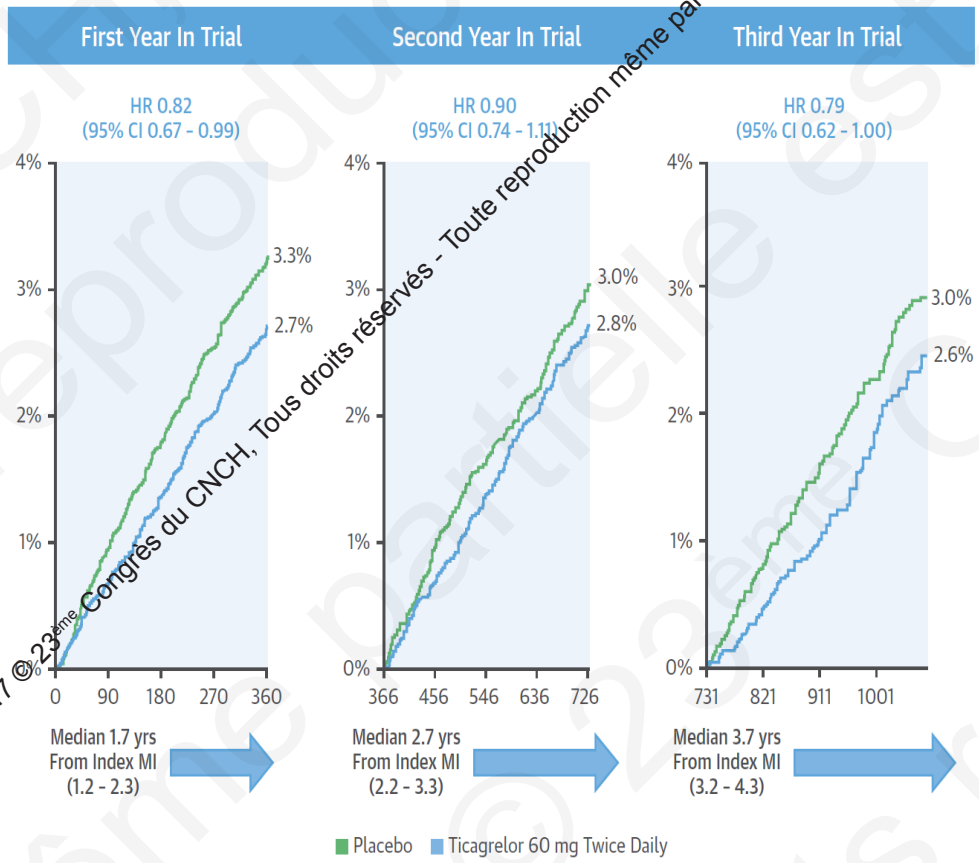


Bonaca MP *et al. Eur Heart J* 2016;37:1133–1142

The increases (versus placebo) in **TIMI major bleeding** were similar for the two ticagrelor dose levels



Bonaca MP *et al. Eur Heart J* 2016;37:1133–1142



Bonaca, M.P. et al. J Am Coll Cardiol. 2017;70(11):1368-75.

Although ticagrelor reduced ischemic risk in patients with prior myocardial infarction (MI), the consistency of its longer-term effects is unknown. In analyzing the rates of cardiovascular death, MI, and stroke (the primary endpoint) at yearly landmarks in the PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis In Myocardial Infarction 54) trial, efficacy of ticagrelor 60 mg remained consistent over time with a trend toward less excess bleeding (safety endpoint). CI = confidence interval; HR = hazard ratio.

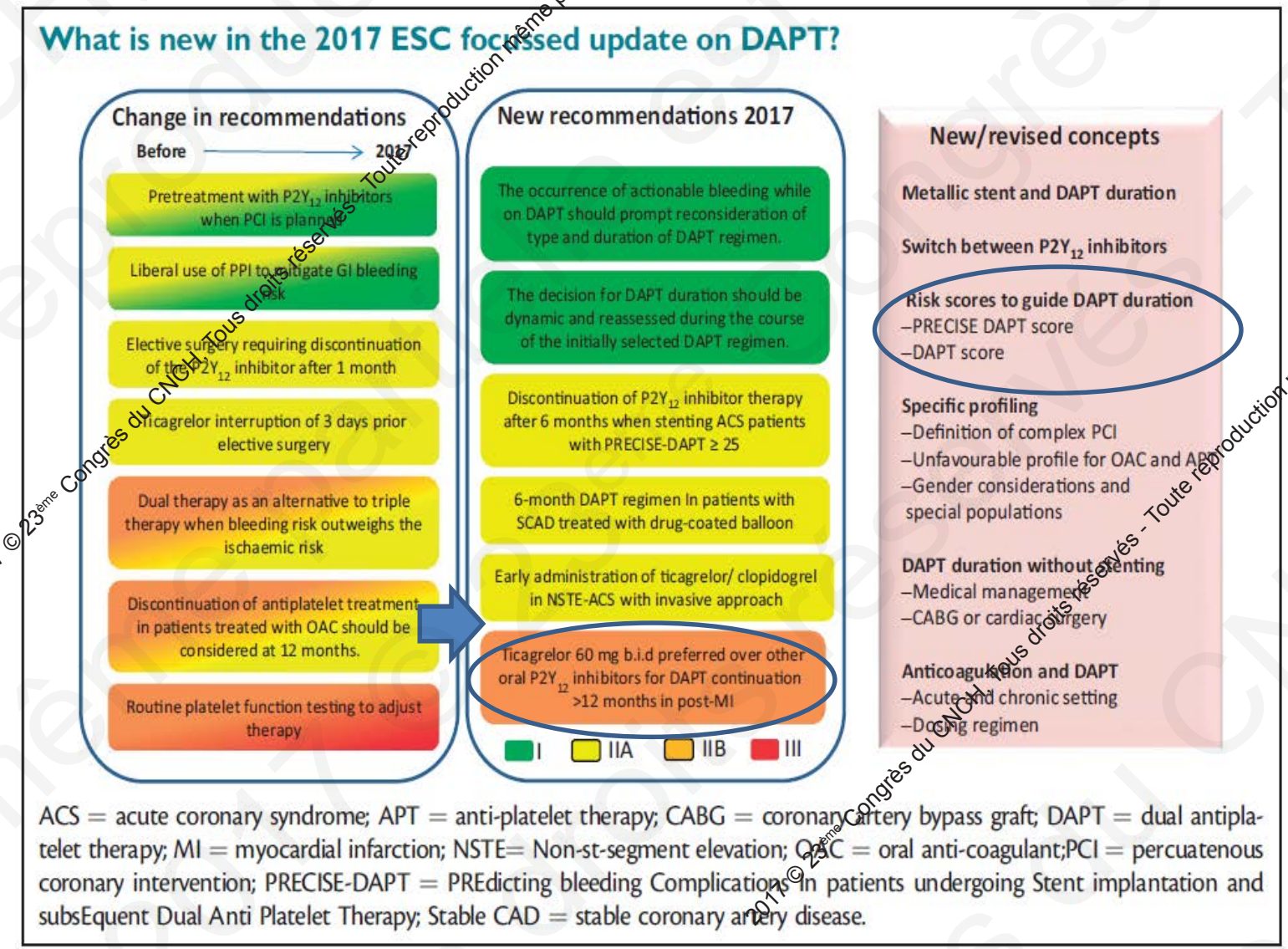
TABLE 2 Safety Outcomes

Year From Randomization	Placebo	Ticagrelor 60 mg	HR (95% CI)
First year	6,996	6,958	
TIMI major	0.27	0.86	3.22 (1.86-5.57)
TIMI major or minor	0.38	1.30	3.48 (2.20-5.50)
TIMI minor	0.11	0.44	4.10 (1.79-9.42)
Intracranial hemorrhage	0.10	0.15	1.61 (0.57-4.56)
Fatal bleeding	0.03	0.11	3.24 (0.66-16.06)
Second year	5,987	5,461	
TIMI major	0.42	0.86	2.07 (1.25-3.43)
TIMI major or minor	0.55	1.13	2.10 (1.35-3.27)
TIMI minor	0.13	0.29	2.36 (0.96-5.78)
Intracranial hemorrhage	0.18	0.18	0.99 (0.40-2.44)
Fatal bleeding	0.13	0.04	0.31 (0.07-1.51)
Third year	4,938	4,447	
TIMI major	0.37	0.60	1.65 (0.84-3.24)
TIMI major or minor	0.50	1.03	2.02 (1.14-3.58)
TIMI minor	0.13	0.45	3.56 (1.16-10.92)
Intracranial hemorrhage	0.20	0.28	1.57 (0.60-4.11)
Fatal bleeding	0.11	0.11	1.09 (0.22-5.40)

Values are n or Kaplan-Meier %, unless otherwise indicated.
TIMI = Thrombolysis In Myocardial Infarction; other abbreviations as in Table 1.

Bonaca, M.P. et al. J Am Coll Cardiol. 2017;70(11):1368–75.

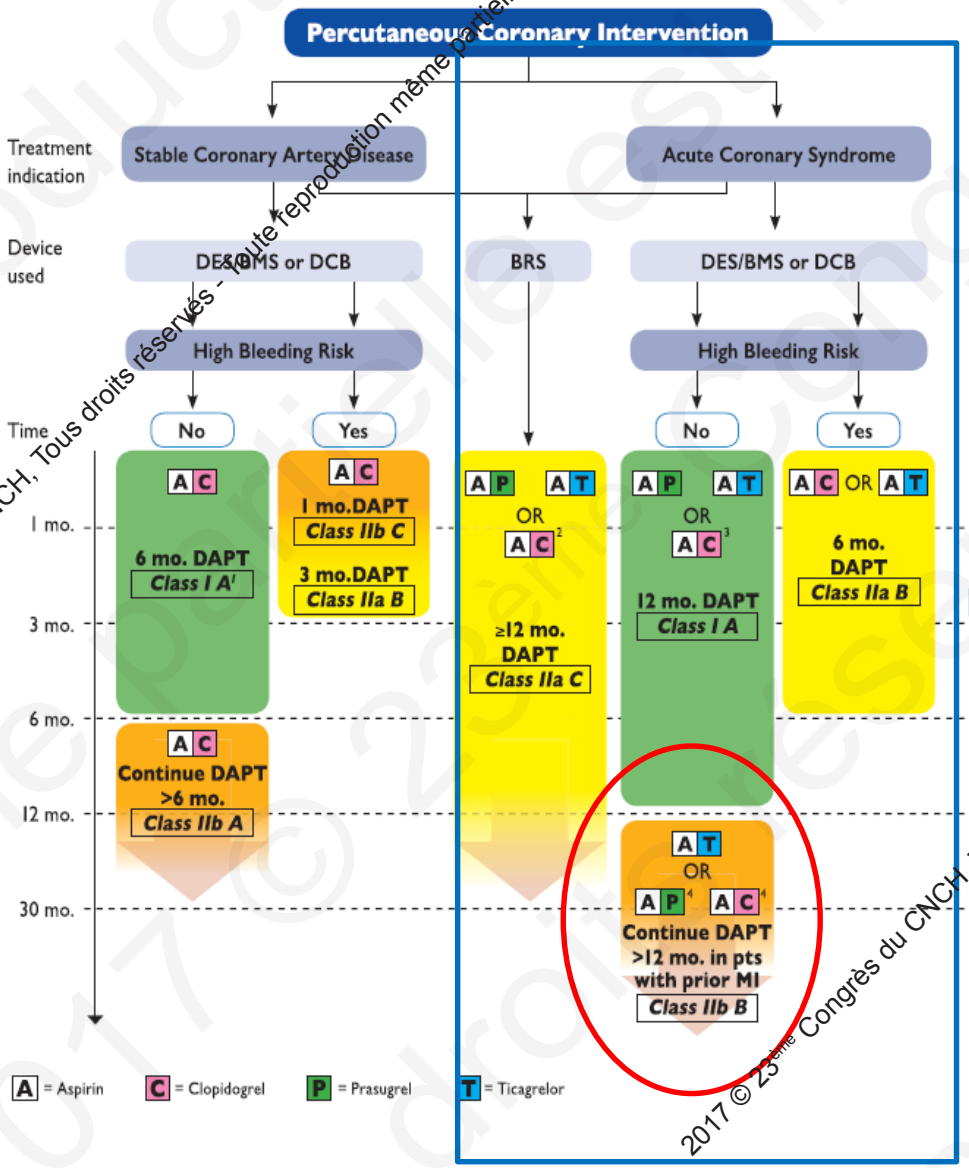
RECOMMANDATIONS ESC 2017



ACS = acute coronary syndrome; APT = anti-platelet therapy; CABG = coronary artery bypass graft; DAPT = dual antiplatelet therapy; MI = myocardial infarction; NSTE= Non-st-segment elevation; OAC = oral anti-coagulant;PCI = percuatenous coronary intervention; PRECISE-DAPT = PREdicting bleeding Complications in patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy; Stable CAD = stable coronary artery disease.

Use of risk scores as guidance for the duration of dual antiplatelet therapy

Recommendations	Class	Level
The use of risk scores designed to evaluate the benefits and risks of different DAPT durations may be considered.	IIb	A



Risque hémorragique

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What is new in 2017 Guidelines on AMI-STEMI *(continued)*

2017 NEW RECOMMENDATIONS

- Additional lipid-lowering therapy if LDL >1.8 mmol/L (70 mg/dL) despite on maximum tolerated statins. ***IMPROVE-IT, FOURIER***
- Complete revascularization during index primary PCI in STEMI patients in shock. Expert opinion

- Cangrelor if $P2Y_{12}$ inhibitors have not been given. ***CHAMPION***
- Switch to potent $P2Y_{12}$ inhibitors 48 hours after fibrinolysis. Expert opinion
- Extend Ticagrelor up to 36 months in high-risk patients. ***PEGASUS-TIMI 54***
- Use of polypill to increase adherence. ***FOCUS***

- Routine use of deferred stenting. ***DANAMI-3-DEFER***

I
IIa
IIb
III

Dual antiplatelet therapy duration in patients with acute coronary syndrome treated with percutaneous coronary intervention (continued)

In patients with ACS who have tolerated DAPT without a bleeding complication, continuation of DAPT for longer than 12 months may be considered.[26,139]	IIb	A
In patients with MI and high ischaemic risk[c] who have tolerated DAPT without a bleeding complication, ticagrelor 60 mg *b.i.d.* for longer than 12 months on top of aspirin may be preferred over clopidogrel or prasugrel.[29,115,142]	IIb	B

ACS = acute coronary syndrome; *b.i.d.* = *bis in die*; DAPT = dual antiplatelet therapy. MI = myocardial infarction; PRECISE-DAPT = PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy.

[a]Class of recommendation.

[b]Level of evidence.

[c]Defined as ≥50 years of age, and one or more of the following additional high-risk features: age of 65 years or older, diabetes mellitus requiring medication, a second prior spontaneous myocardial infarction, multivessel coronary artery disease, or chronic renal dysfunction, defined as an estimated creatinine clearance < 60 mL/min.

These recommendations refer to stents that are supported by large-scale randomized trials with clinical endpoint evaluation leading to unconditional CE mark, as detailed in Byrne *et al.*[134]

conclusion

- Évaluation du **risque résiduel**:
  - Point critique de prise en charge
  - Place des scores de risque : PRECISE-DAPT (< 12 mois) et DAPT (> 12 mois)
  - Intégration des critères PEGASUS pour évaluer la durée de la DAPT++
  - Lutter contre le mauvais contrôle des facteurs de risque, le niveau de prévention secondaire insuffisant et la diffusion de la maladie athéromateuse
- Stratégie thérapeutique plus agressive:
  - statines à fortes doses,
  - DAPT prolongée
- Questions en suspens: monothérapie plus puissante que l'aspirine (à quelles doses?)

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