Un changement de paradigme dans la prise en charge des patients atteints de maladie athéroscléreuse

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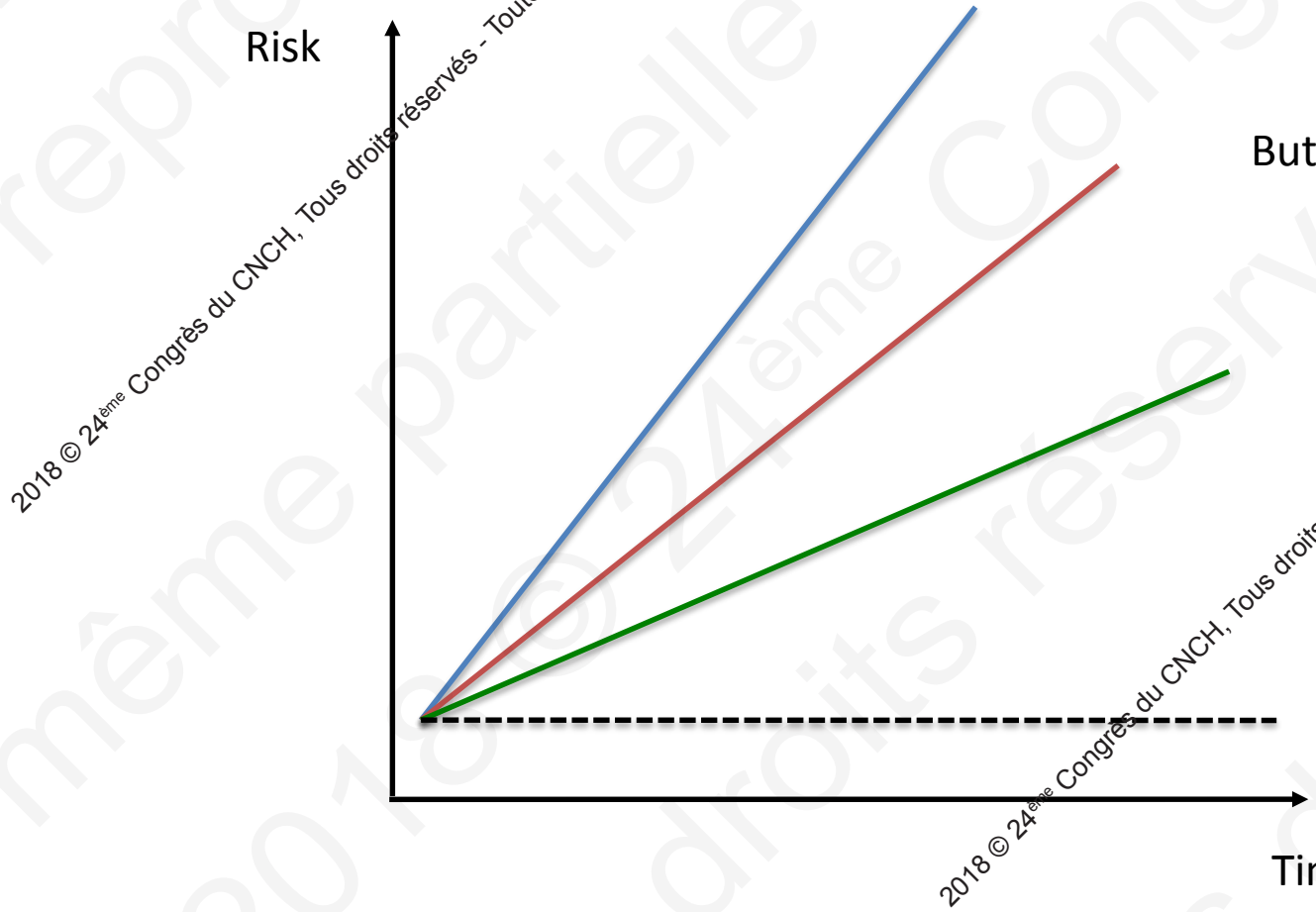
The concept of stable CAD and residual risk



Stable = linear curve
But the slope may still be high

Virtual curve of the absence of risk

The residual ischemic risk

Risk of MI

CORONOR Registry

Variable	SHR	95% CI	p value
Current smoker	1.87	1.27 – 2.77	0.002
LDL-cholesterol (per 10 mg/dL)	1.06	1.02 – 1.11	0.007
Prior coronary bypass	0.53	0.32 – 0.86	0.011
Multi-vessel CAD	1.53	1.08 – 2.15	0.015
Diabetes mellitus with HbA1c > 7%	1.62	1.09 – 2.40	0.016
Persistent angina at inclusion	1.70	1.06 – 2.73	0.028

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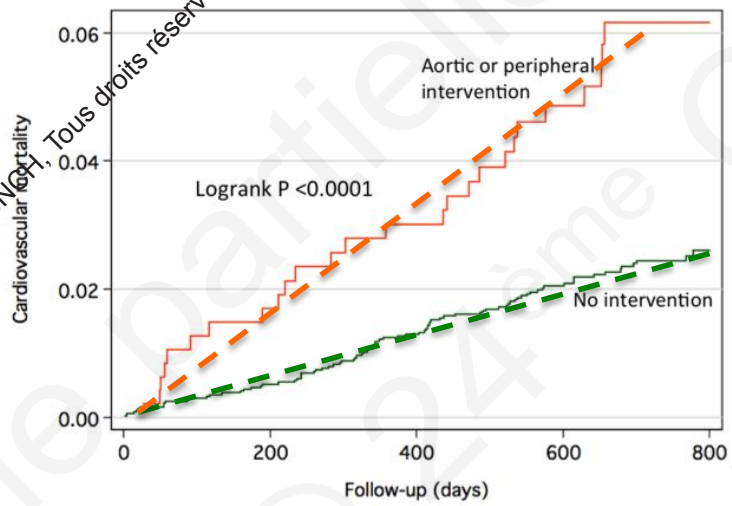
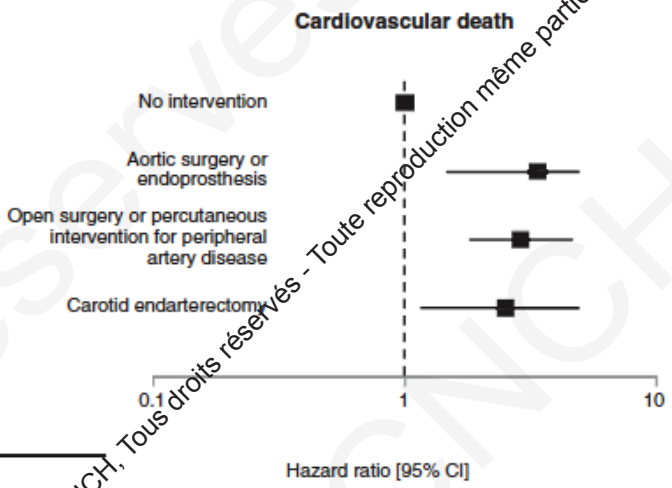
The residual ischemic risk

Risk of the composite CV death, MI, Stroke

CORONOR Registry

History of non-coronary vascular intervention





	Unadjusted		Adjusted	
	HR (95% CI)	p value	HR (95% CI)	p value
All-cause death	2.13 (1.59–2.86)	<0.0001	1.55 (1.13–2.13)	0.007
Cardiovascular death	2.53 (1.65–3.86)	<0.0001	1.98 (1.24–3.15)	0.004
Non cardiovascular death	1.84 (1.22–2.78)	0.004	1.26 (0.81–1.96)	0.303
Cardiovascular death, myocardial infarction or stroke	2.08 (1.51–2.86)	<0.0001	1.71 (1.24–2.43)	0.003

Delsart et al. Eur J Prevent. Cardiol. 2015:22;864-71

The CLARIFY Risk Model for CV death and MI

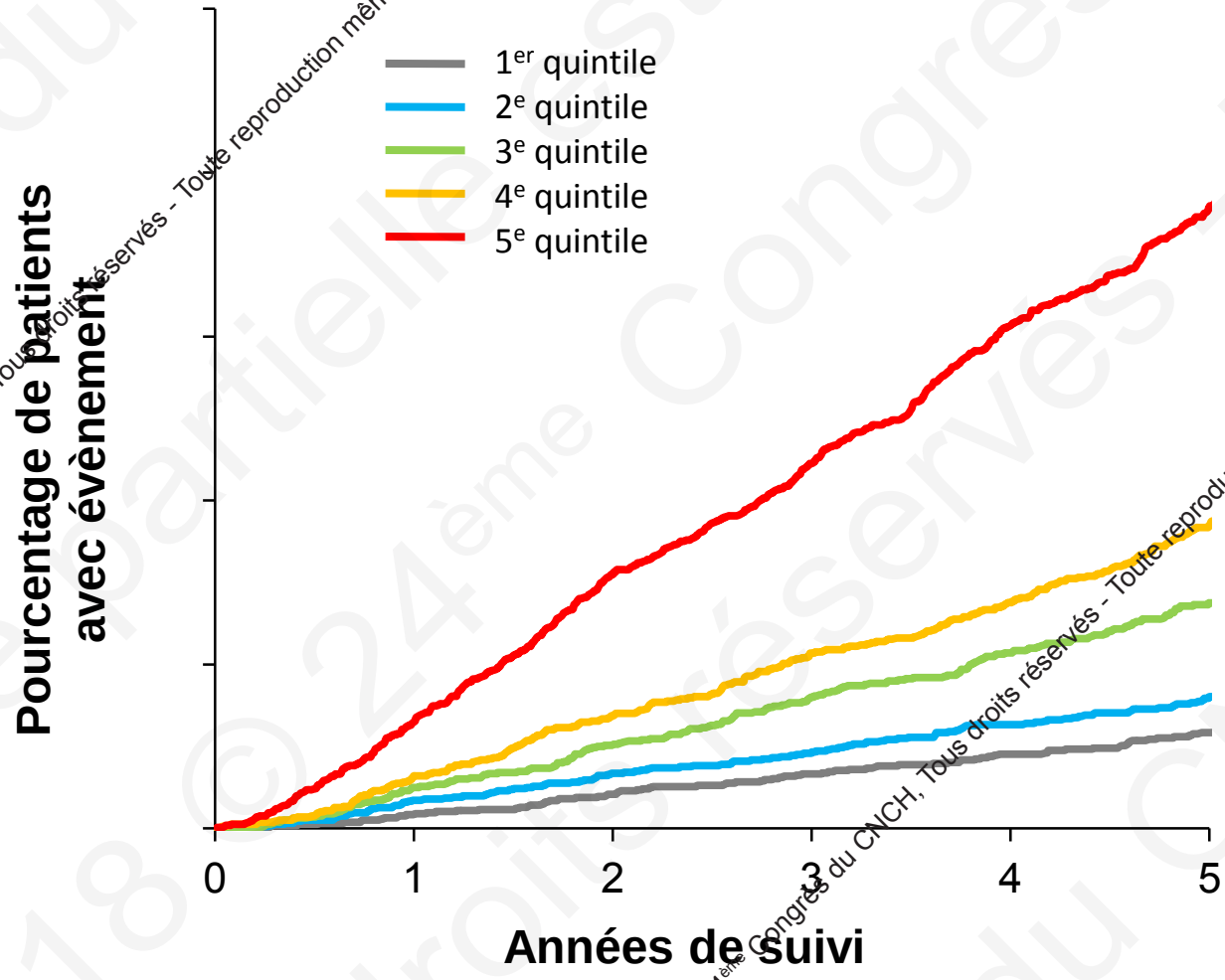
CLARIFY Registry

12 variables associated with the risk of CV death and MI

Predictor	Category	HR (95% CI)	P for HR	Overall P-value*
Age per 5 year increase		1.19 (1.15, 1.23)	<0.0001	
Diabetes	Insulin dependent	1.88 (1.58, 2.25)	<0.0001	
(referent non-diabetic)	Not insulin dependent	1.30 (1.14, 1.48)	0.0001	
Smoking status	Current	1.67 (1.39, 2.01)	<0.0001	<0.0001
(referent Never)	Former	1.33 (1.17, 1.51)	<0.0001	
Current Angina	Yes	1.32 (1.17, 1.50)	<0.0001	
AF/Flutter	Yes	1.54 (1.31, 1.82)	<0.0001	
Myocardial Infarction	Yes	1.29 (1.13, 1.47)	0.0001	
Peripheral Arterial Disease	Yes	1.26 (1.08, 1.48)	0.0029	
PCI/CABG	Yes	0.78 (0.69, 0.88)	0.0001	
Stroke	Yes	1.51 (1.23, 1.84)	<0.0001	
Hospitalisation for CHF	Yes	1.73 (1.46, 2.04)	<0.0001	
eGFR (ml/min per 1.73 m2)	<30	2.73 (2.06, 3.61)	<0.0001	<0.0001
(referent 60-90)	30 - 44.99	1.53 (1.26, 1.87)	<0.0001	
	45 - 59.99	1.27 (1.09, 1.48)	0.0022	
	>=90	1.10 (0.94, 1.30)	0.24	
LVEF	< 48%	1.85 (1.54, 2.22)	<0.0001	<0.0001
(referent [55 – 60])%)	48 - 54.9%	1.35 (1.11, 1.65)	0.0031	
	60 - 64.9%	1.16 (0.95, 1.42)	0.15	
	>= 65%	1.01 (0.82, 1.24)	0.94	

ESC 2018 - D'après Ford I et al., LB Registry 2980

Incidence cumulée du critère combiné mortalité cardiovasculaire et infarctus du myocarde, par quintiles de distribution du score de risque dans la population CLARIFY (n = 15,770)



ESC 2018 - D'après Ford I et al., LB Registry 2980

Prévention de l'athérothrombose par les anticoagulants
A l'époque des AVK …

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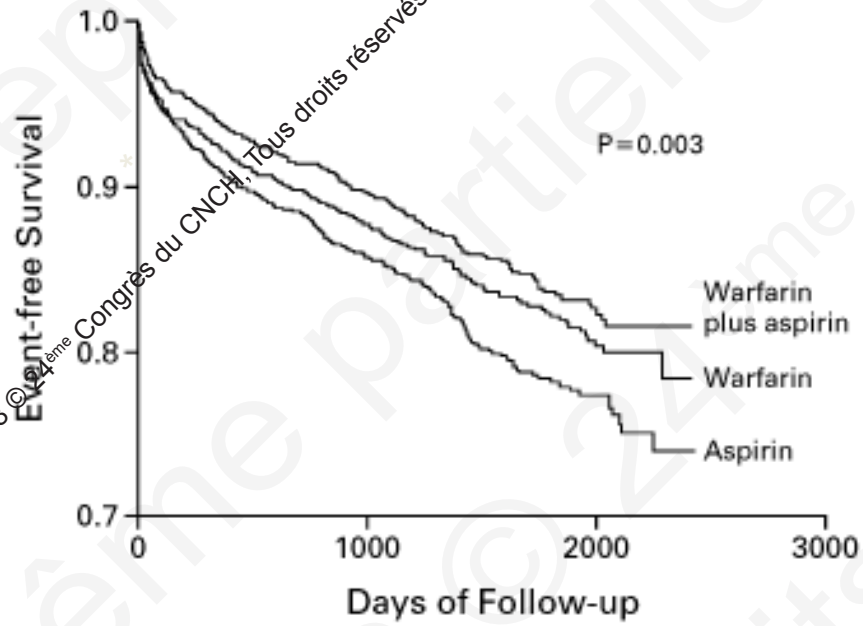
Warfarin in Secondary Prevention

WARIS II Trial

N= 3,630 post MI patients randomized to aspirin (160 mg daily), warfarin (INR 2.8-4.2), or warfarin (INR 2.0-2.5) plus aspirin (75 mg daily)

for a mean of 4 years



*Composite of death, reinfarction, and stroke

Type of Bleeding	A (n)	W (n)	W + A (n)
Cerebral	1	5	3
GI	6	18	21
Other	1	7	4
Total	8	33	28
Rate**	0.17 %	0.62 %	0.62%

**p<0.001

Warfarin plus aspirin reduces the rate of adverse events with a higher rate of major bleeding

Hurlen M et al. NEJM 2002

Prévention de l'athérothrombose par les anticoagulants
A l'époque des AOD …

Les données sur la faible dose de rivaroxaban …

En post-SCA
Et dans le cadre de la maladie coronaire chronique

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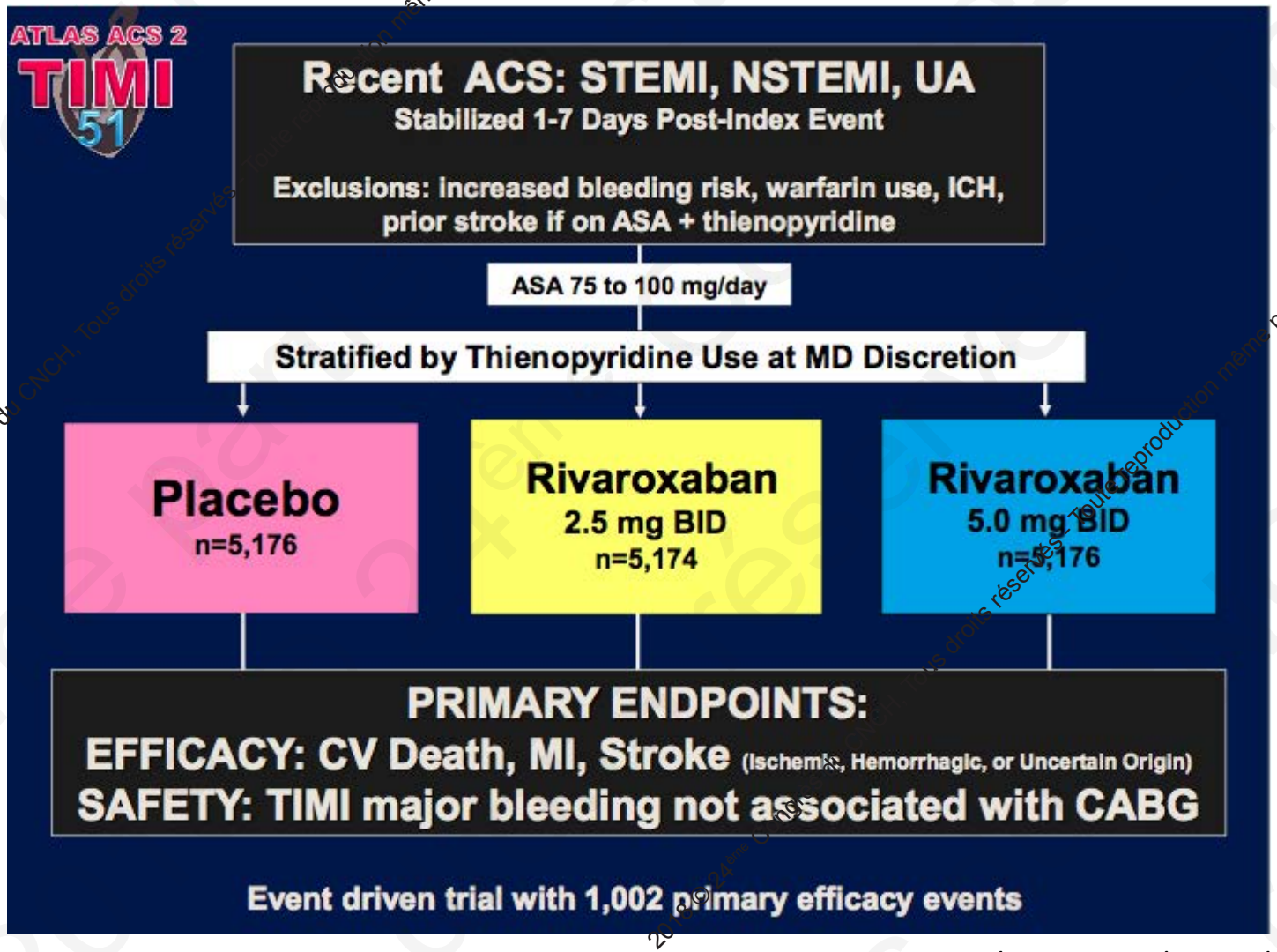
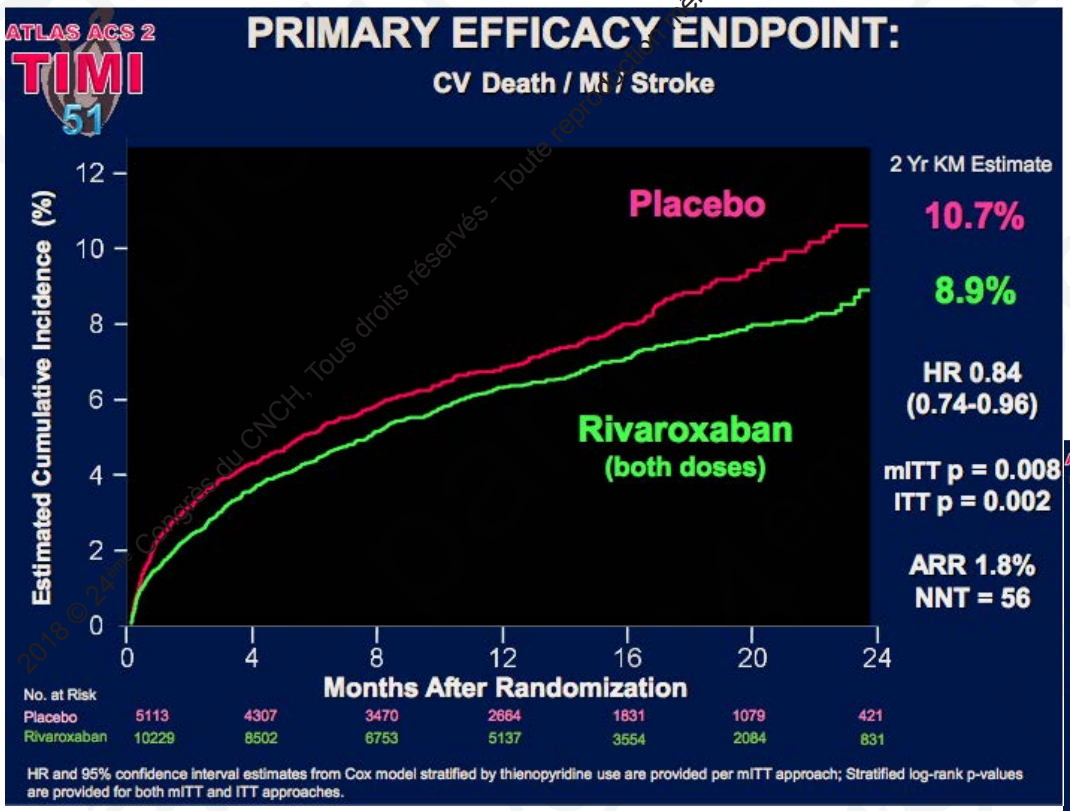
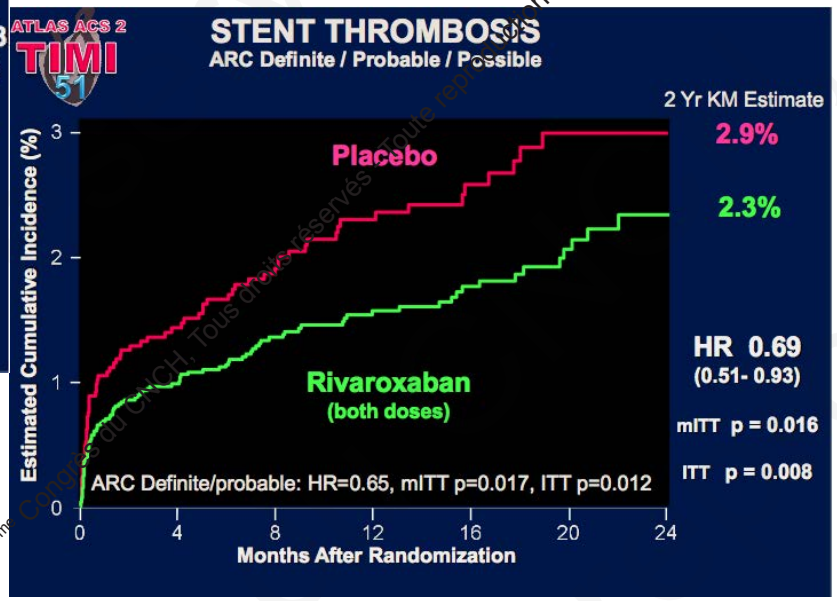
Le post SCA : ATLAS



Gibson M, et al. N Engl J Med 2005.

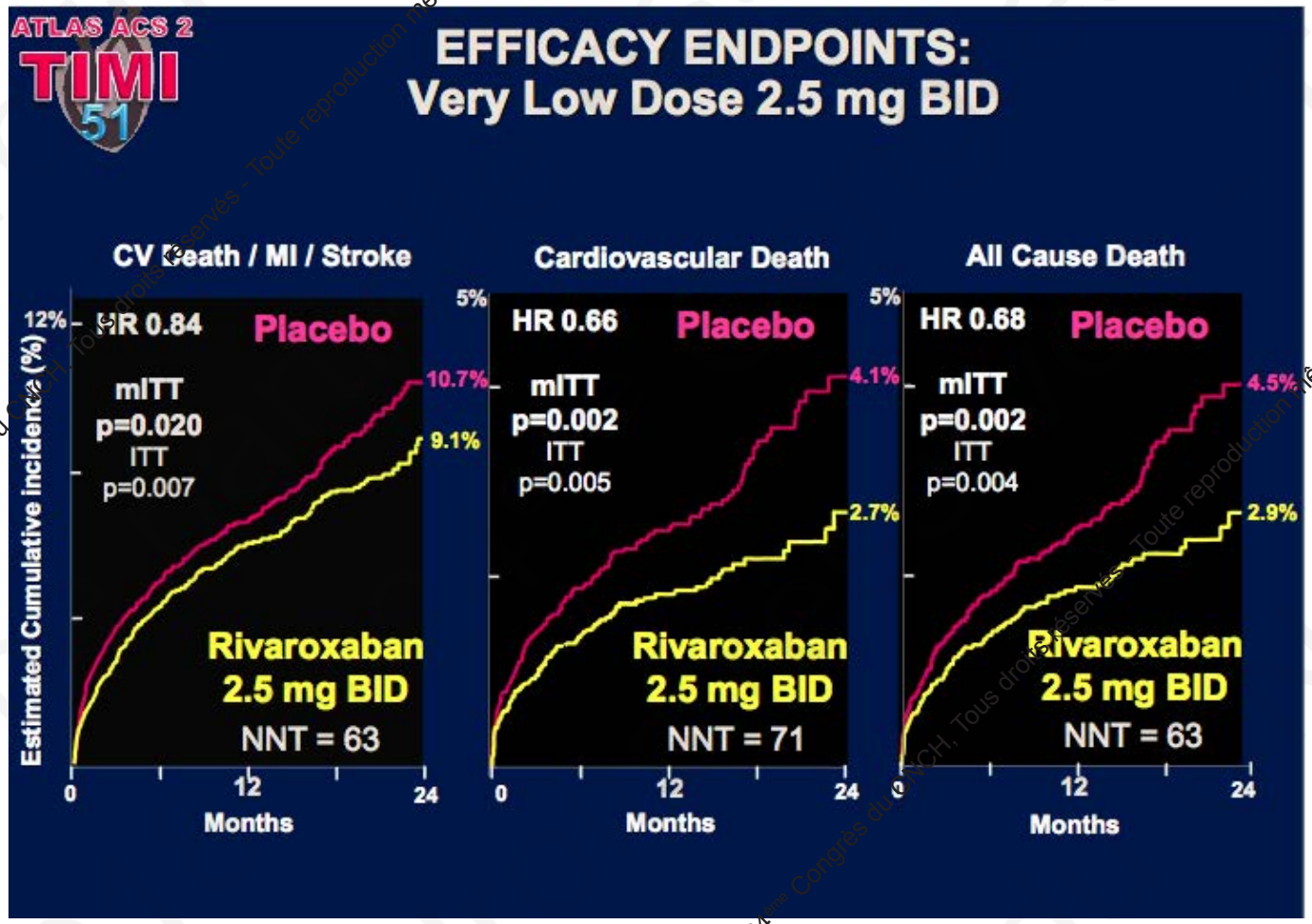
Le post SCA : ATLAS





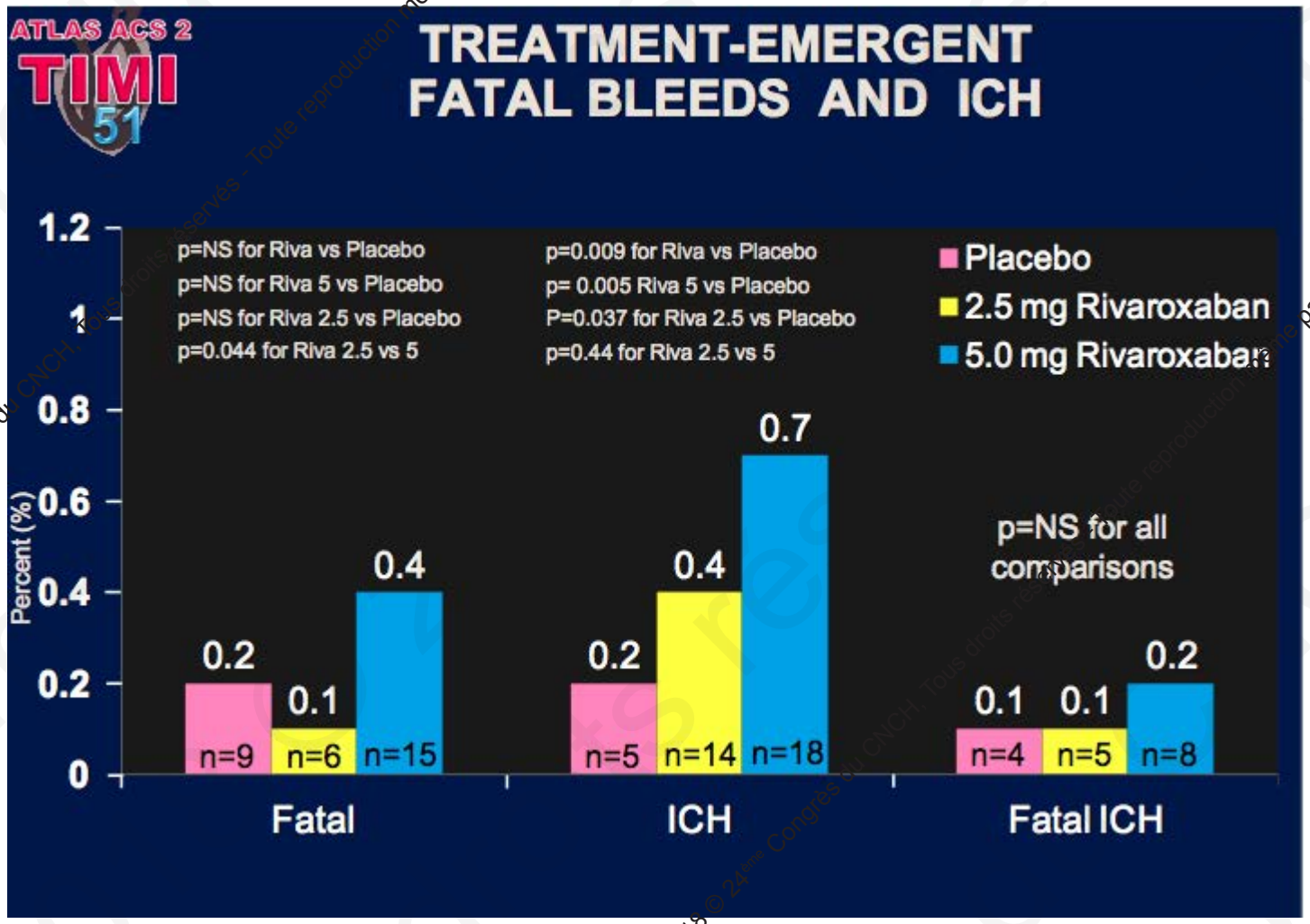
Gibson M, et al. N Engl J Med 2005.

Le post SCA : ATLAS



Gibson M, et al. N Engl J Med 2005.

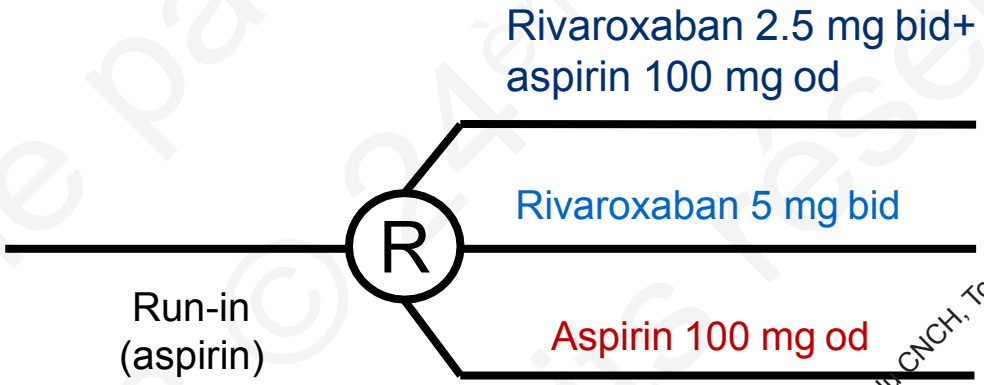
Le post SCA : ATLAS



Gibson M, et al. N Engl J Med 2005.

La maladie coronaire chronique : COMPASS

Stable CAD or PAD
2,200 with a primary outcome event



Eikelboom J, et al. N Engl J Med 2017

COMPASS

Key inclusion criteria

- PAD
- CAD with ≥1 of:
  - Aged ≥65 years
  - Aged <65 years plus atherosclerosis in ≥2 vascular beds or ≥2 additional risk factors
    - Current smoker
    - Diabetes mellitus
    - Renal dysfunction (eGFR <60 ml/min)
    - Heart failure
    - Non-lacunar ischaemic stroke ≥1 month ago

Key exclusion criteria

- Stroke ≤1 month or any haemorrhagic or lacunar stroke
- Severe HF with known ejection fraction <30% or NYHA class III or IV symptoms
- **Need for DAPT, other non-aspirin antiplatelet therapy, or OAC therapy**
- eGFR <15 ml/min

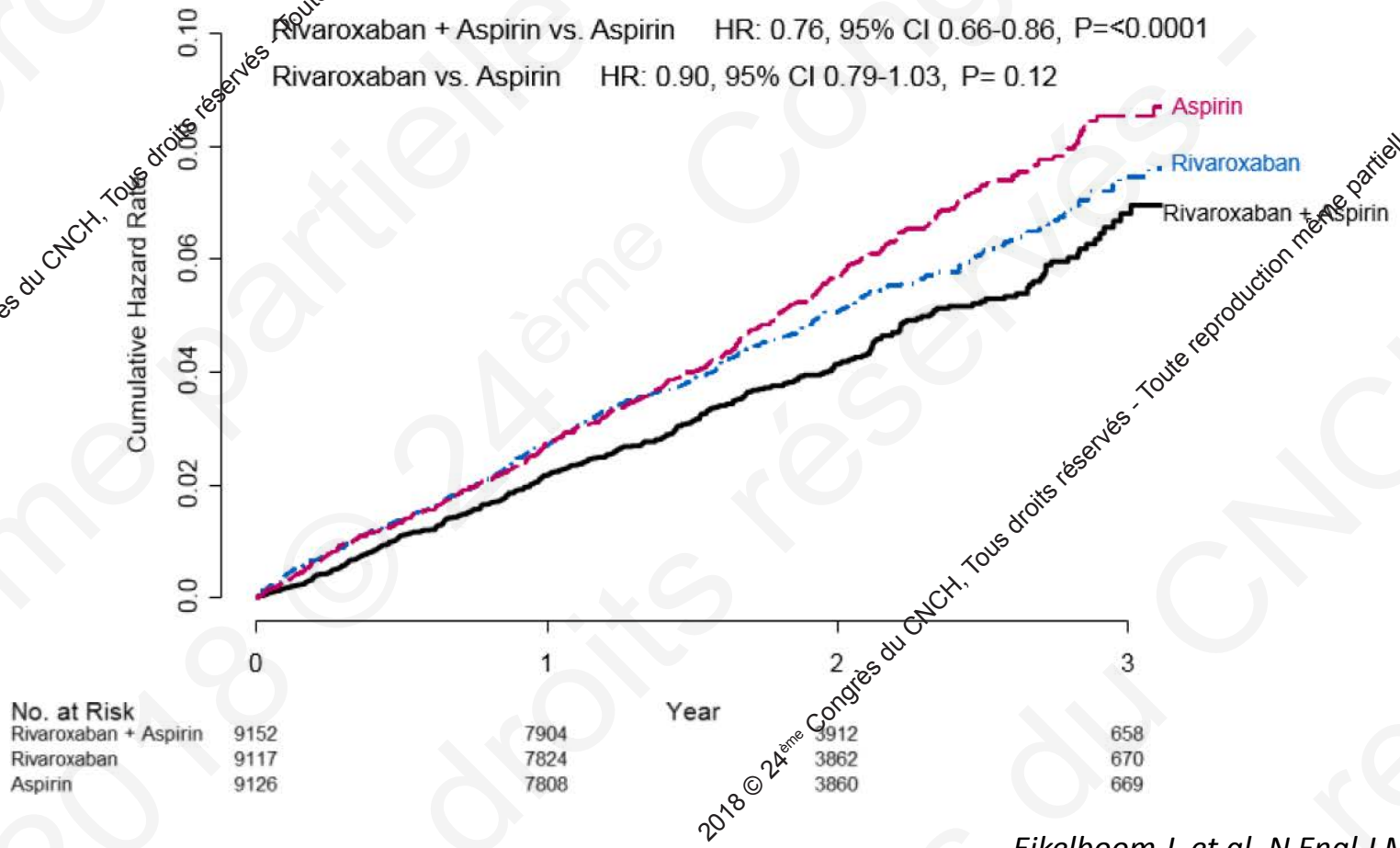
Eikelboom JW *et al*, *N Engl J Med* 2017;377:1319–1330

n=27,395 patients with stable atherosclerotic vascular disease (CAD or PAD)

CAD 90.6%

Prior MI 62%, 7.1 mean years since Prior MI

PAD 27.3%



Eikelboom J, et al. N Engl J Med 2017

Primary and Secondary components

Outcome	R + A N=9,152	A N=9,126	Rivaroxaban + Aspirin vs. Aspirin	
	N (%)	N (%)	HR (95% CI)	p
CV death	160 (1.7%)	203 (2.2%)	0.78 (0.64-0.96)	0.02
Stroke	83 (0.9%)	142 (1.6%)	0.58 (0.44-0.76)	<0.0001
MI	178 (1.9%)	205 (2.2%)	0.86 (0.70-1.05)	0.14
Mortality	313 (3.4%)	378 (4.1%)	0.82 (0.71-0.96)	0.01

Eikelboom J, et al. N Engl J Med 2017

Major bleeding

Outcome	R + A N=9,152	R N=9,117	A N=9,126	Rivaroxaban + Aspirin vs. Aspirin		Rivaroxaban vs. Aspirin	
	N (%)	N (%)	N (%)	HR (95% CI)	P	HR (95% CI)	P
Major bleeding	288 (3.1%)	255 (2.8%)	170 (1.9%)	1.70 (1.40-2.05)	<0.0001	1.51 (1.25-1.84)	<0.0001
Fatal	15 (0.2%)	14 (0.2%)	10 (0.1%)	1.49 (0.67-3.33)	0.32	1.40 (0.62-3.15)	0.41
Non fatal ICH*	21 (0.2%)	32 (0.4%)	19 (0.2%)	1.10 (0.59-2.04)	0.77	1.69 (0.96-2.98)	0.07
Non-fatal other critical organ*	42 (0.5%)	45 (0.5%)	29 (0.3%)	1.43 (0.89-2.29)	0.14	1.57 (0.98-2.50)	0.06

* symptomatic

Eikelboom J, et al. N Engl J Med 2017

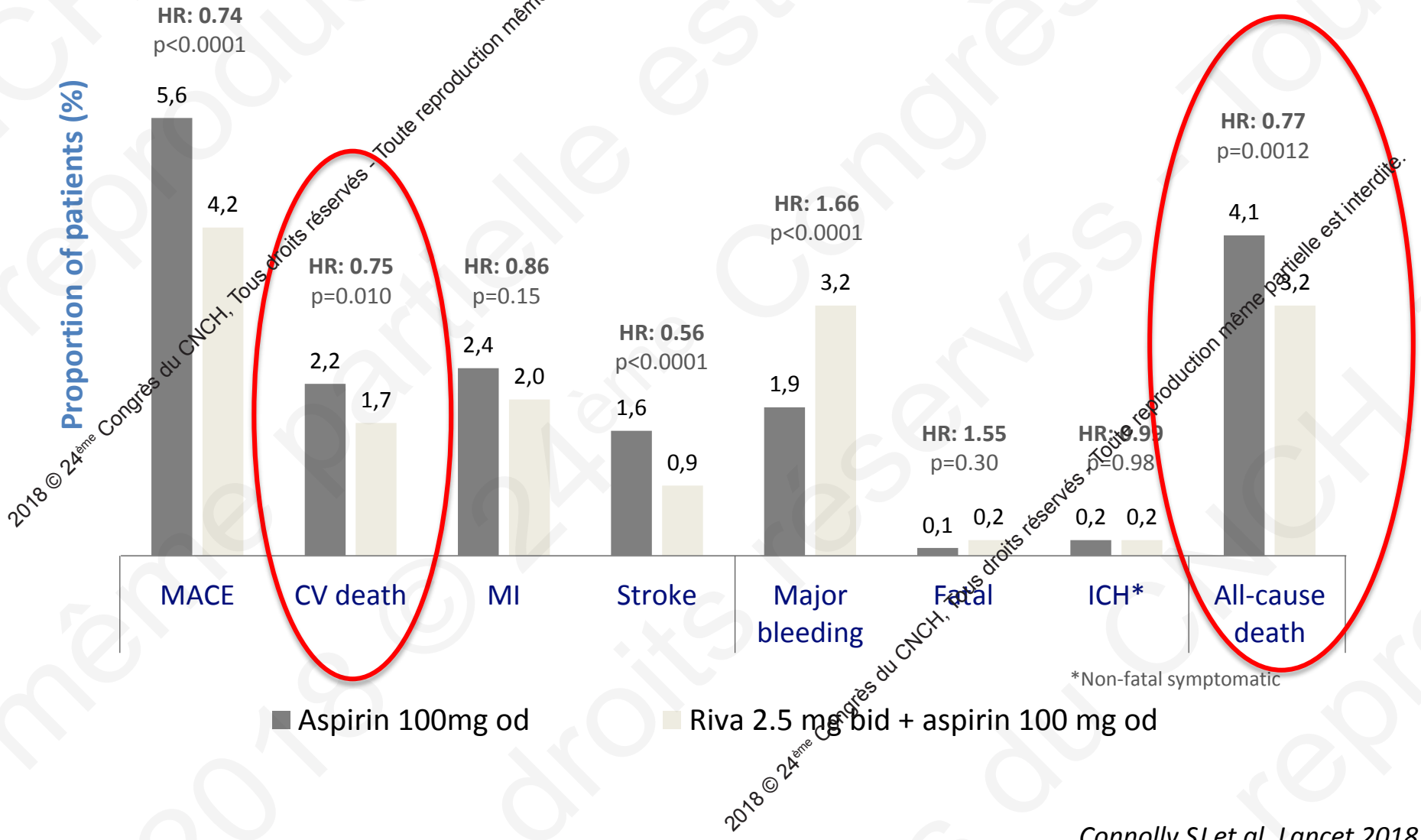
Net clinical benefit

Outcome	R + A N=9,152	A N=9,126	Rivaroxaban + Aspirin vs. Aspirin	
	N (%)	N (%)	HR (95% CI)	P
Net clinical benefit (Primary + Severe bleeding events)	431 (4.7%)	534 (5.9%)	0.80 (0.70-0.91)	0.0005

Eikelboom J, et al. N Engl J Med 2017

COMPASS Trial in CAD patients

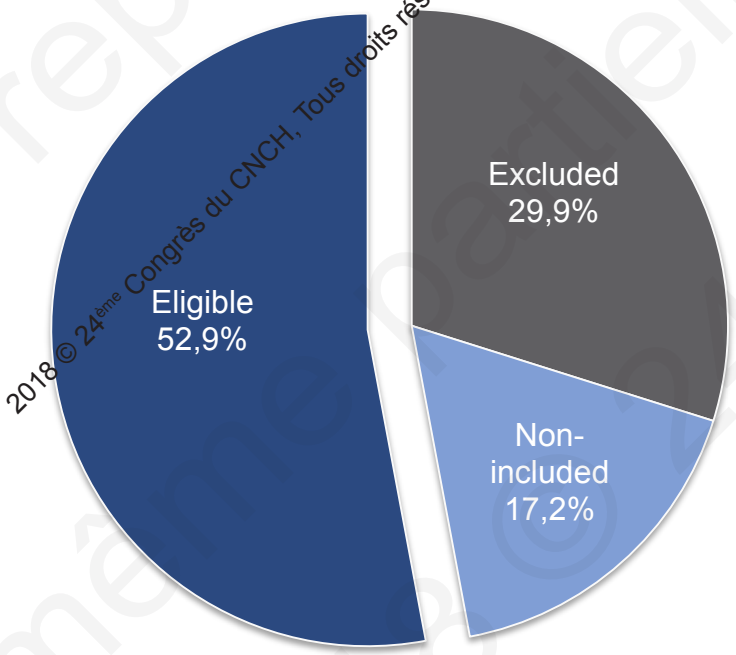
n=24,824 patients with stable coronary artery disease (CAD)



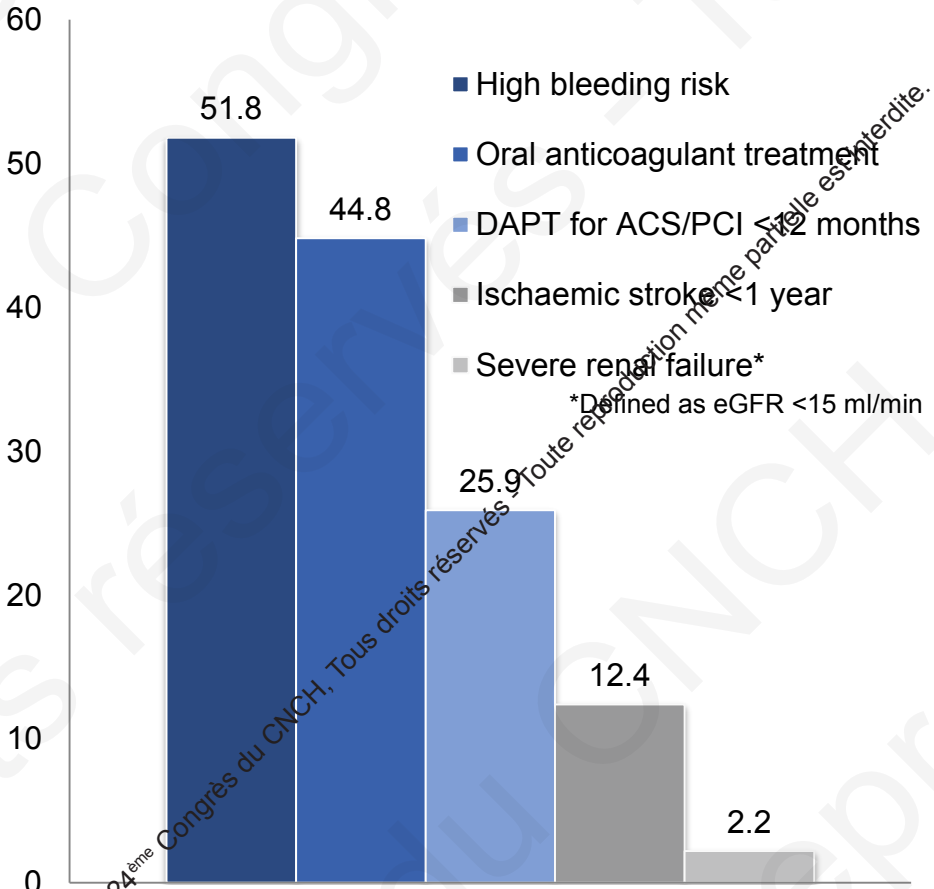
Connolly SJ et al. Lancet 2018

COMPASS CAD Trial in the Real World

Eligibility for the COMPASS Trial Among 31,873 Evaluable REACH Registry Patients



Main Reasons for Being Excluded (%)



Darmon A et al. Eur Heart J. 2017

COMPASS Trial in PAD patients

N=7,740 patients with stable peripheral artery disease (PAD)

	Low-dose rivaroxaban plus aspirin (n=2492)	Rivaroxaban alone (n=2474)	Aspirin alone (n=2504)
History of PAD			
Previous aorta-femoral or lower extremity bypass surgery, PTA of iliac, or infrainguinal artery	668 (26·8)	703 (28·4)	674 (26·9)
History of intermittent claudication and ABI <0·90 or substantial peripheral arterial stenosis ≥50%	1142 (45·8)	1120 (45·3)	1140 (45·5)
Previous limb or foot amputation	116 (4·7)	107 (4·3)	112 (4·5)
Symptomatic PAD of lower extremities*	1409 (56·5)	1361 (55·0)	1359 (54·3)
Carotid artery disease†	617 (24·8)	622 (25·1)	680 (27·2)
Symptomatic PAD‡	2026 (81·3)	1983 (80·1)	2039 (81·4)
CAD and ABI <0·90§	466 (18·7)	491 (19·8)	465 (18·6)

*Defined as intermittent claudication with ABI <0·90 or stenosis of ≥50%; or previous aorta-femoral or lower extremity bypass surgery, percutaneous transluminal angioplasty of iliac or infrainguinal arteries, or limb or foot amputation for arterial vascular disease. †Defined as previous carotid endarterectomy or stent or asymptomatic carotid artery stenosis of ≥50%. ‡Symptomatic PAD is the sum of symptomatic PAD of lower extremities and carotid artery disease. §Asymptomatic PAD of lower extremities.

Table 1: Baseline characteristics

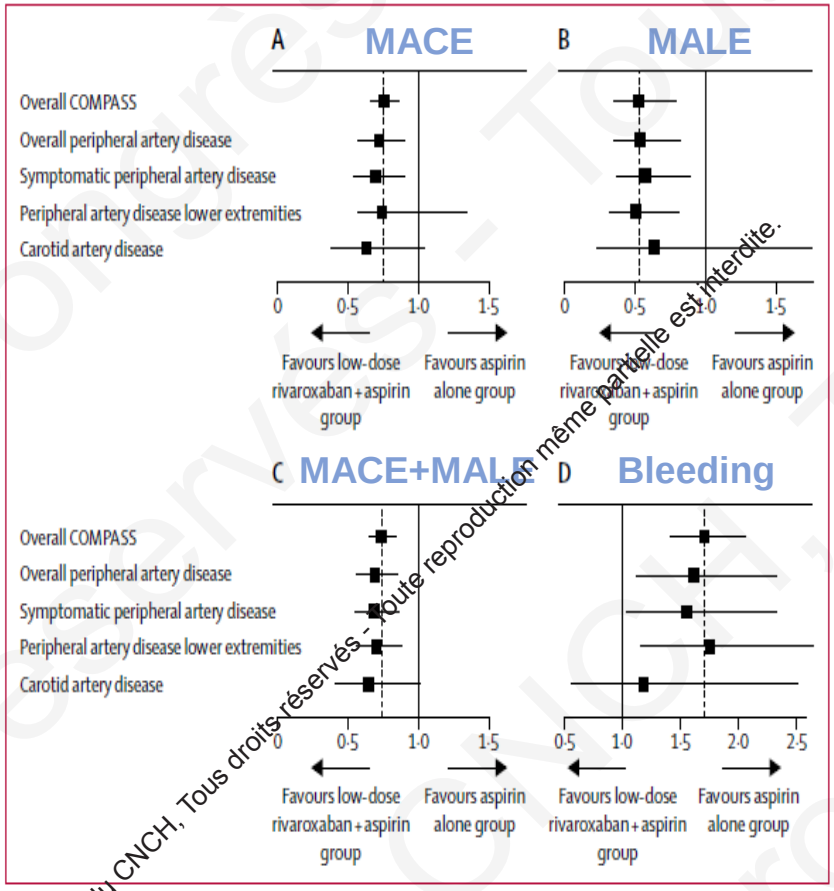


Figure 4: Analyses of primary and secondary outcomes

Hazard ratios and 95% CI are shown for all subgroups of patients with peripheral artery disease for major adverse cardiovascular events (A) and major adverse limb events including major amputation (B), major adverse cardiovascular or limb events including major amputation (C) and for major bleeding (D). The dotted line indicates the point estimate for the overall COMPASS trial population (n=27 395).

Anand S et al, Lancet 2018;391:219–229

Conclusion

- **Rivaroxaban 2.5 mg bid + aspirin** reduces ischemic events with an increase in major bleeding, but **provides a net clinical benefit**
- **Rivaroxaban 2.5 mg bid + aspirin** reduces **CV and all-cause mortality**
- **The benefit of the dual pathway strategy** in CAD patients is transferrable to the **real world practice**
- Patients selection based on the presence of **high CV risk features** and **low risk for bleeding**

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AMM Européenne (23 août 2018)

Xarelto (2.5 mg 2X/j), co-administré avec de l'acide acétylsalicylique (AAS) 75-100 mg/j, est indiqué pour la prévention des événements athérothrombotiques chez les patients adultes présentant une maladie coronarienne ou une maladie artérielle périphérique symptomatique à haut risque d'événements ischémiques

The US FDA (October 11th, 2018)

Rivaroxaban (Xarelto®), 2.5 mg twice daily, plus aspirin low dose once daily to reduce the risk of major cardiovascular events including cardiovascular (CV) death, heart attack or stroke in patients with chronic coronary artery disease (CAD) or peripheral artery disease (PAD).

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