Les anticorps monoclonaux anti-PCSK9 : pour quels patients ?

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Dr Farnier reports having received grants, consulting fees and/or honoraria and delivering lectures for Abbott/Mylan, Akcea/Ionis, Amgen, AstraZeneca, Eli Lilly, Kowa, Merck and Co, Pfizer, Roche, Sanofi/Regeneron and Servier

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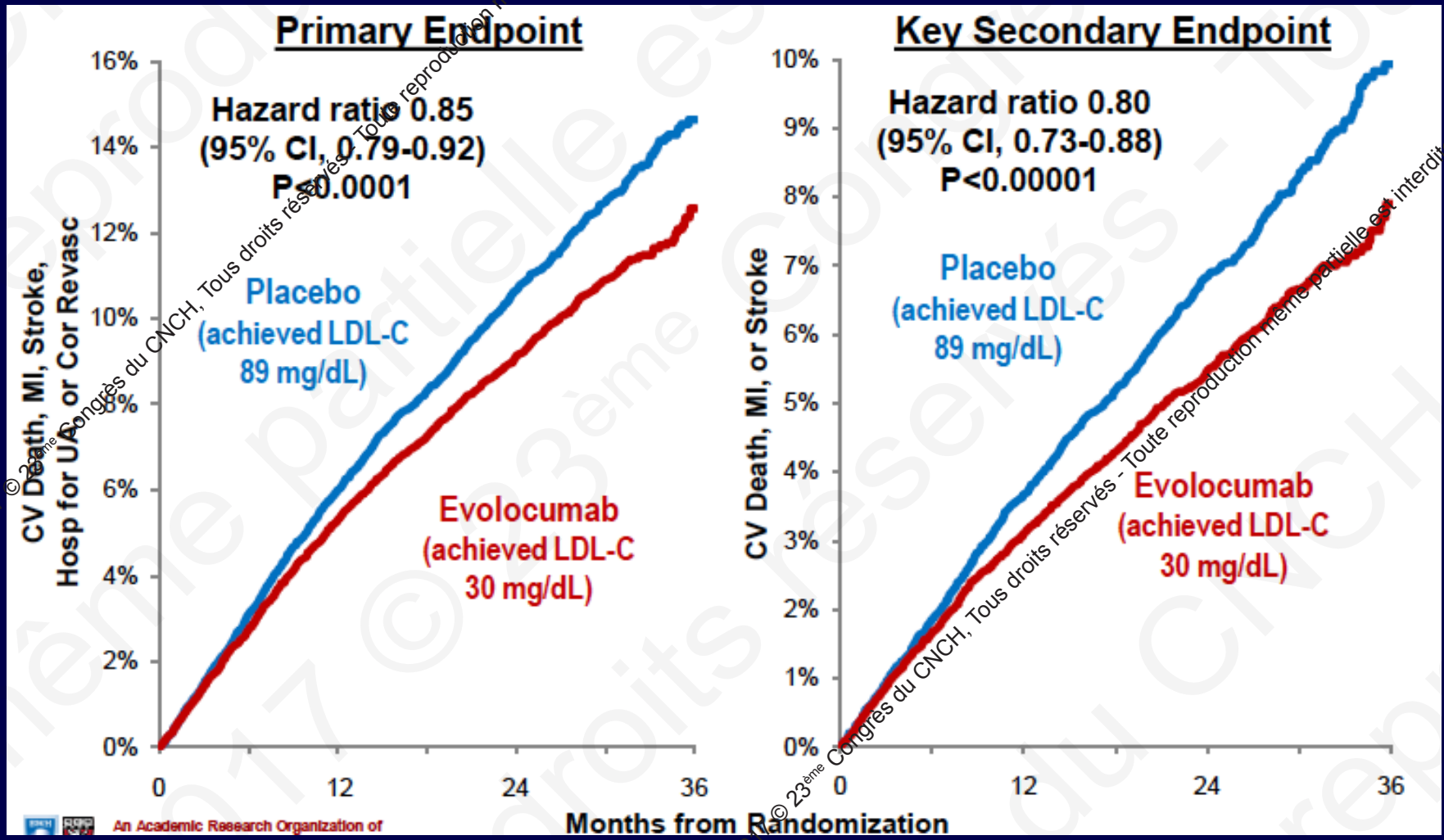
Inhibiteurs de PCSK9 : pour quels patients ?

- Interprétation des résultats de FOURIER
- Identification des patients prioritaires
- Propositions d'un Consensus Européen

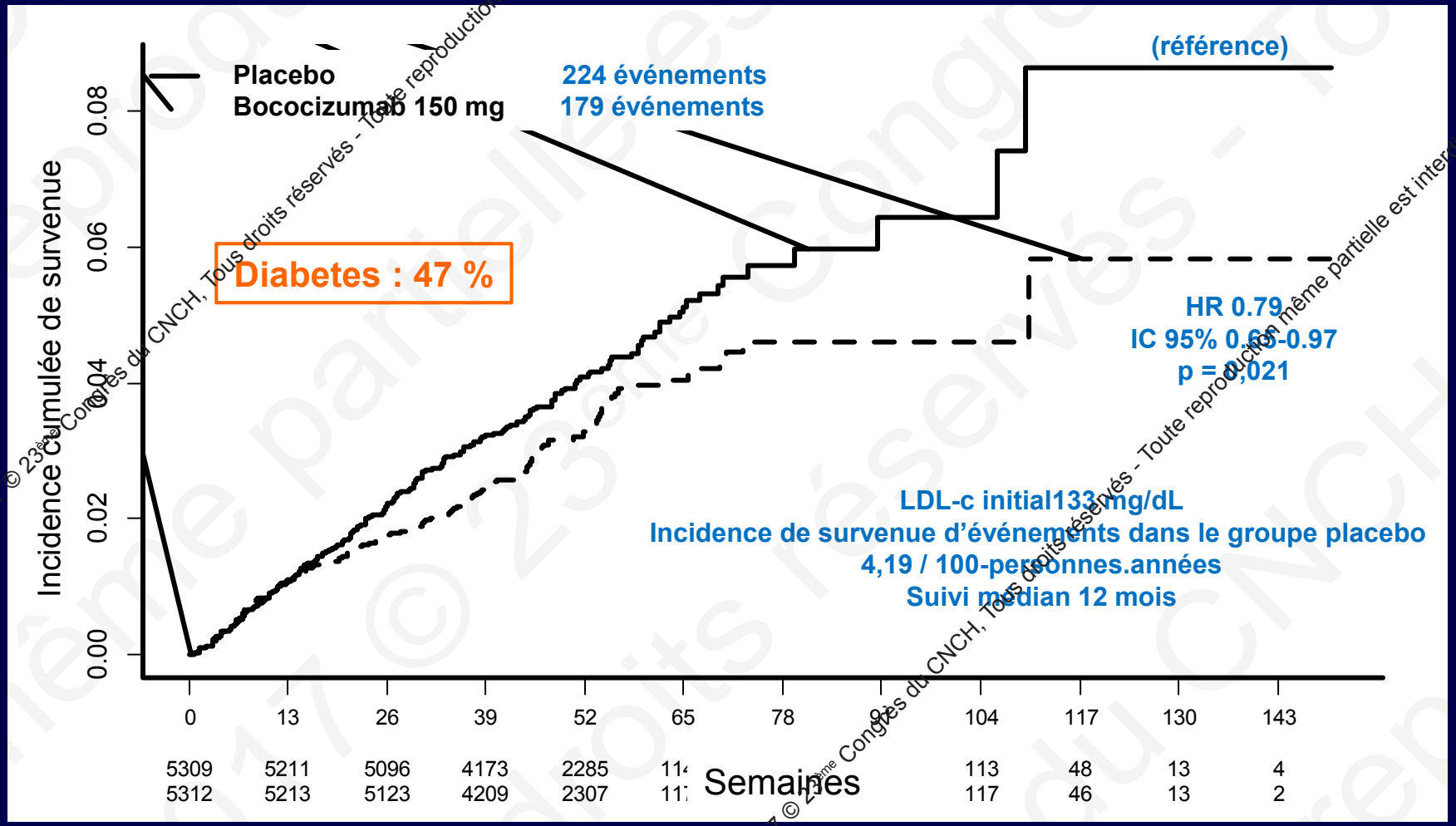
Etude FOURIER : efficacité de l'évolocumab



Sabatine et al. N Engl J Med. 2017; 376: 1713-22

Etude SPIRE-2 : critère principal*

(inclusion : LDL-C > 100 mg/dL))



* IDM non fatal, AVC non fatal, hospitalisation pour angor instable avec nécessité de revascularisation urgente ou décès CV

Ridker et al. N Engl J Med. 2017; 376: 1527-39

European Heart Journal (2017) **0**, 1–6
doi:10.1093/eurheartj/ehx450

CURRENT OPINION

Reduction of low density lipoprotein-cholesterol and cardiovascular events with proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors and statins: an analysis of FOURIER, SPIRE, and the Cholesterol Treatment Trialists Collaboration

Brian A. Ference[1], Christopher P. Cannon[2], Ulf Landmesser[3], Thomas F. Lüscher[4], Alberico L. Catapano[5]*†, and Kausik K. Ray[6]†

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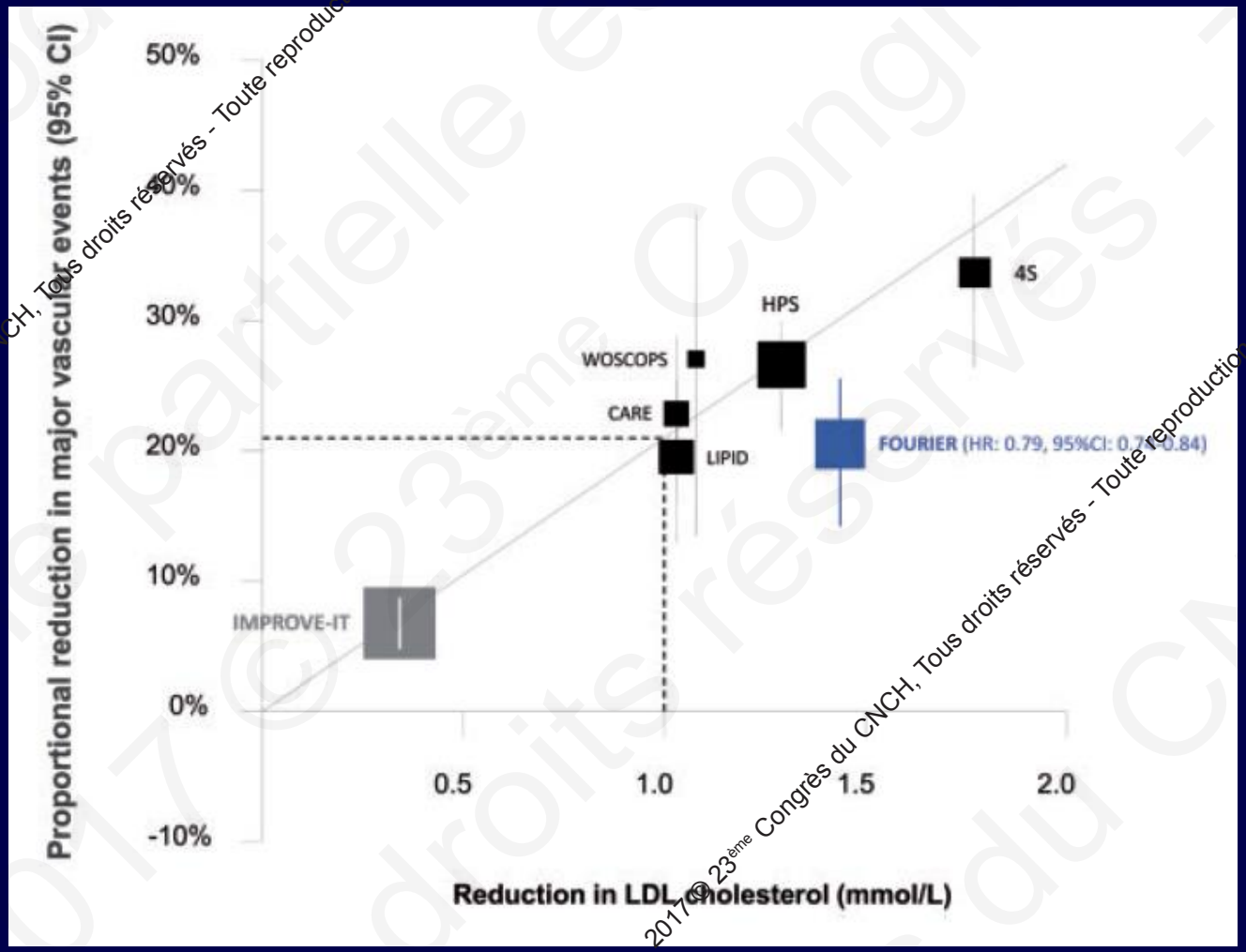
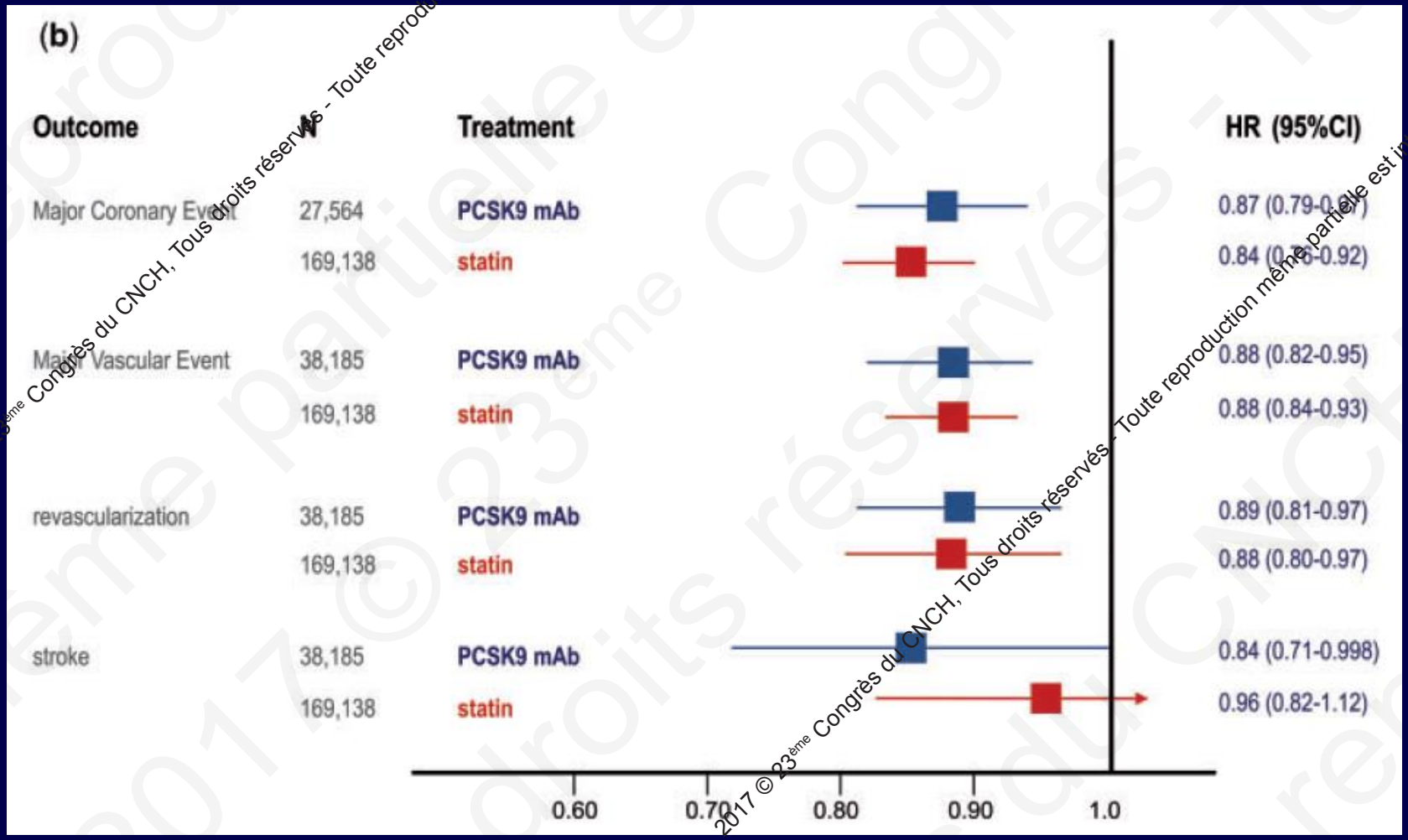
Effect of 2.2 years of treatment with evolocumab on risk of major vascular events as compared to 5 years of treatment with a statin



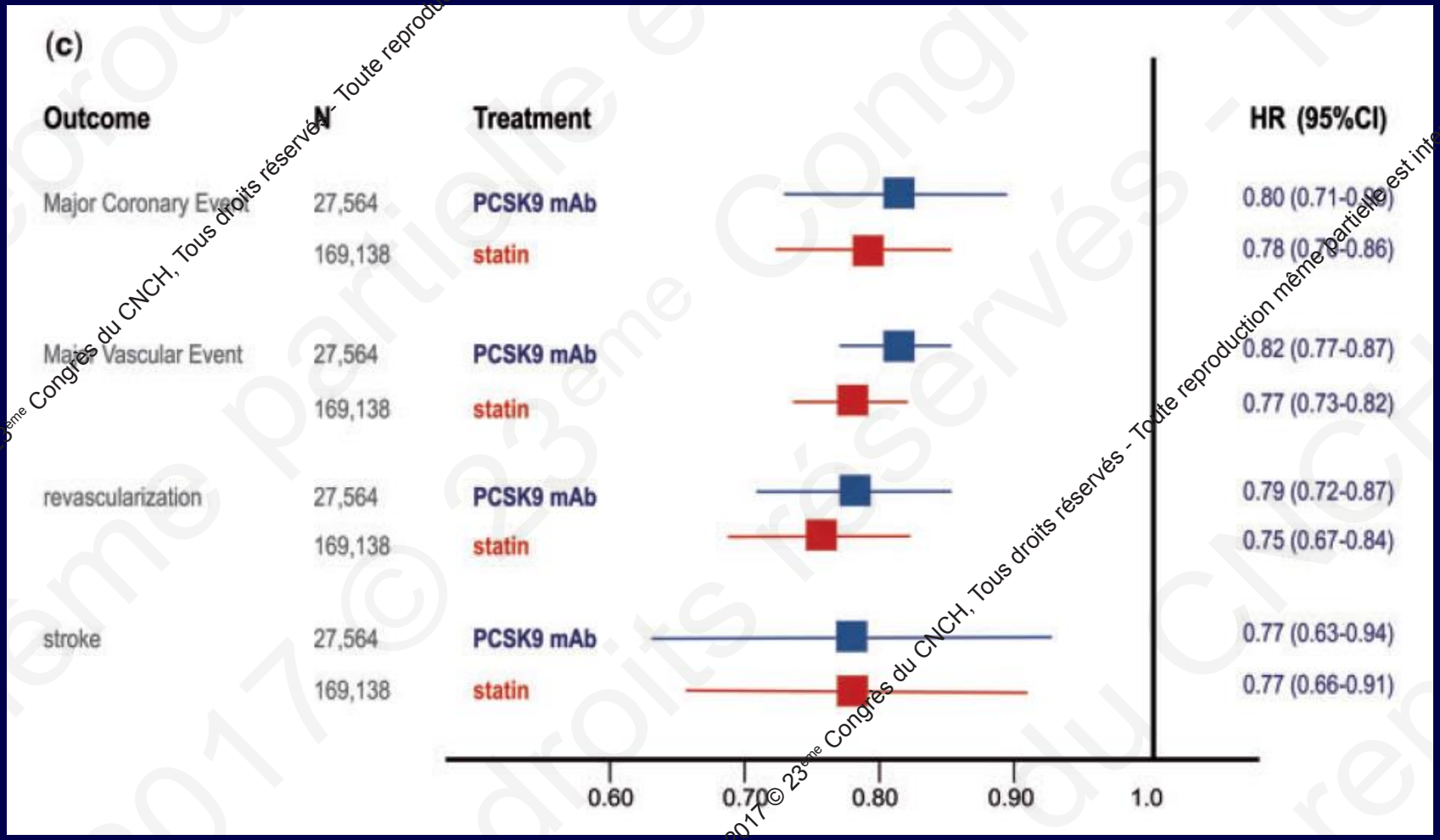
Ference et al. Eur Heart J 2017: online

Effect of PCSK9 inhibitors per mmol/L reduction in LDL-C in a meta-analysis of the FOURIER and SPIRE-2 trials during the first year of treatment compared with the effect of statins during the first year of treatment per mmol/l reduction in LDL-C as reported by the CTT



Ference et al. Eur Heart J 2017: online

Effect of PCSK9 inhibitors in the FOURIER trial per mmol/l reduction in LDL-C during the second year of treatment as compared to the effect of statins during the second year of treatment per mmol/L reduction in LDL-C as reported by the CTT



Ference et al. Eur Heart J 2017: online

KEY FINDINGS

- For every 1 mmol/L of LDL-C reduction the relative risk reduction (RRR) of major vascular events achieved :

  - For 1 year of treatment was :
    - in ***SPIRE 2 = 14 %***
    - in ***CTT with statins = 12 %***

  - For 2 years of treatment was :
    - in ***FOURIER = 17 %***
    - in ***CTT with statins = 17 %***

Ference et al. Eur Heart J 2017: online

Inhibiteurs de PCSK9 : pour quels patients ?

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Quels patients prioritaires ?

Medical rationale
(*absolute CV risk*)
and
cost effectiveness

Who are the very high-risk patients that benefit the most from non-statin agents ?

Objective : identification of patients with the highest CV risk on maximum tolerated LLT

Challenge : assessment for severe risk (extreme risk)

2 main categories :

- Patients with ASCVD
- Patients with FH

ASCVD = atherosclerotic cardiovascular disease; LLT = lipid lowering therapy

Who are the very high-risk patients that benefit the most from non-statin agents ?

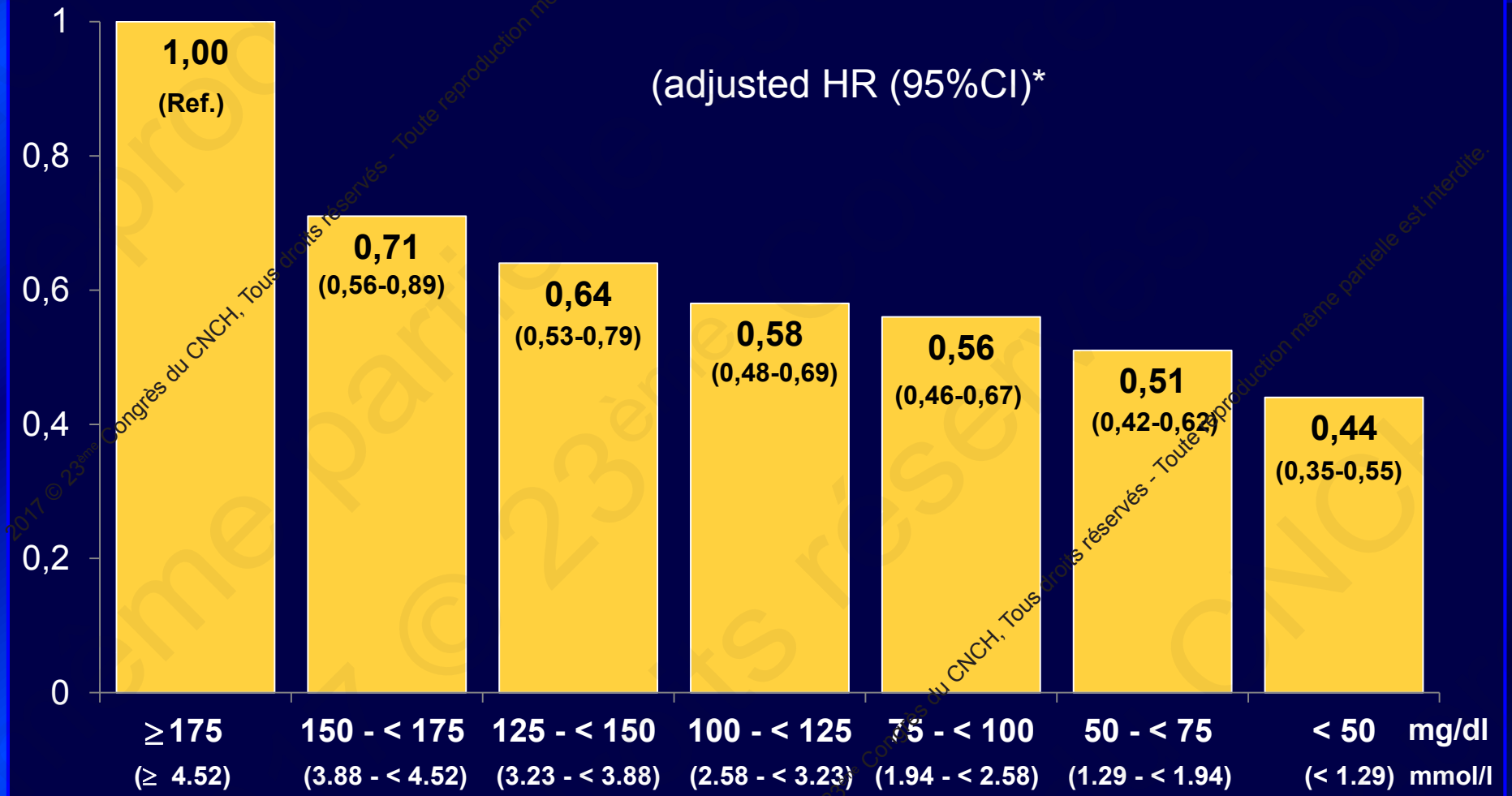
Patients with ASCVD

- LDL-C levels ?
- Patient groups ?
  - Recurrent, polyvascular
  - CABG
  - Diabetes
  - …
- Risk scores ?

FH patients

- With ASCVD
- Homozygous FH
- « Severe » heterozygous FH without clinical ASCVD

Risk for Major CV Events by Achieved on-Trial LDL-C levels



** Adjusted for sex, age, smoking status, presence of DM, SBP, HDL-C and trial*

Boekholdt et al. JACC 2014; 64: 485-494

Patients with Recurrent Disease : MI

*PEGASUS trial : 3-year KM rates for CV events**

Subgroup	Patients	Ticagrelor 90 mg 3 Year KM (%)	Ticagrelor 60 mg 3 Year KM (%)	Placebo 3 Year KM (%)
Second prior MI				
Second MI	3,499	14.68	13.65	15.21
No Second MI	17,662	6.53	6.59	7.79

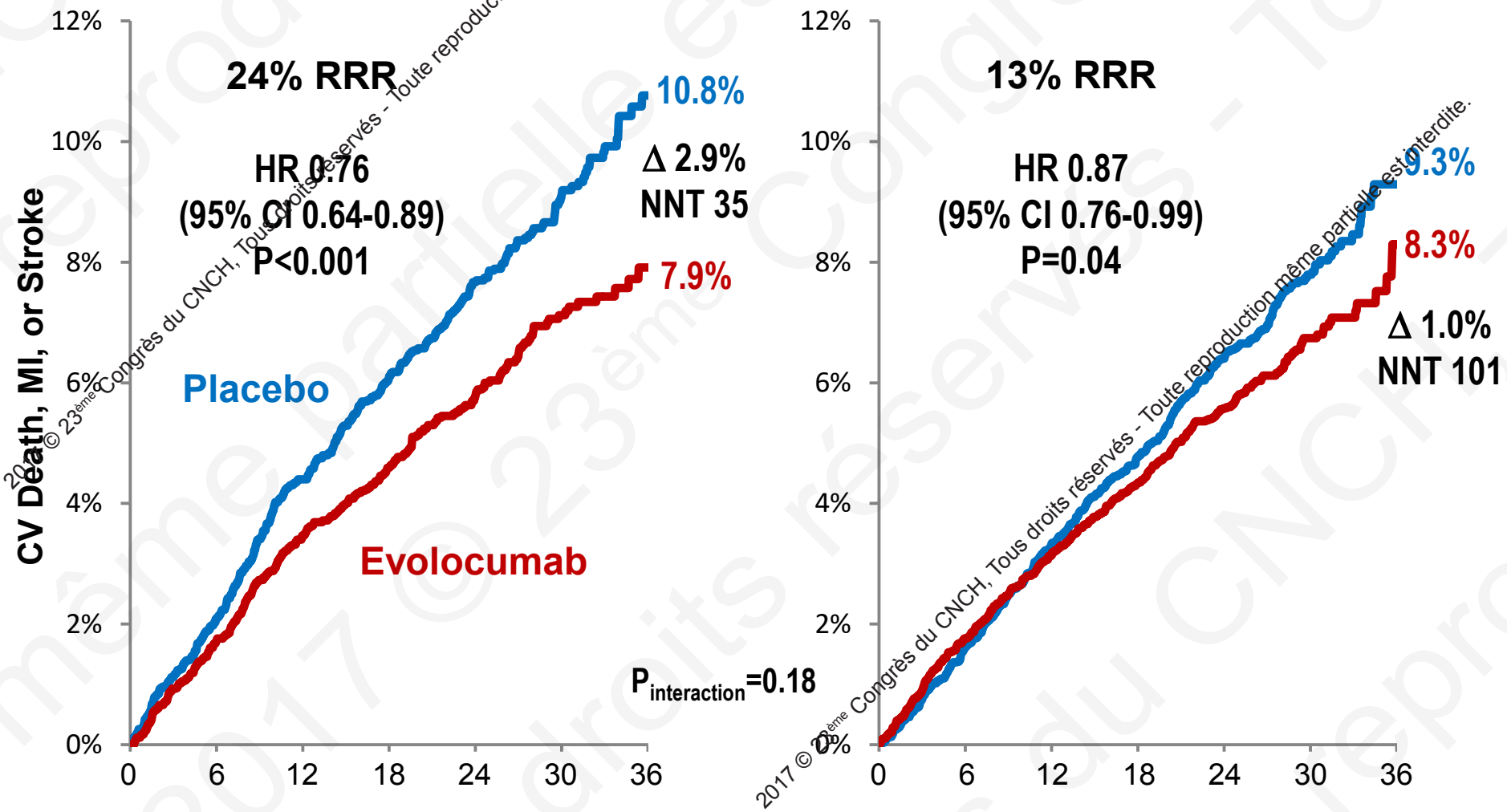
* CV death, MI, or stroke

Bonaca et al. NEJM 2015; March 14: online

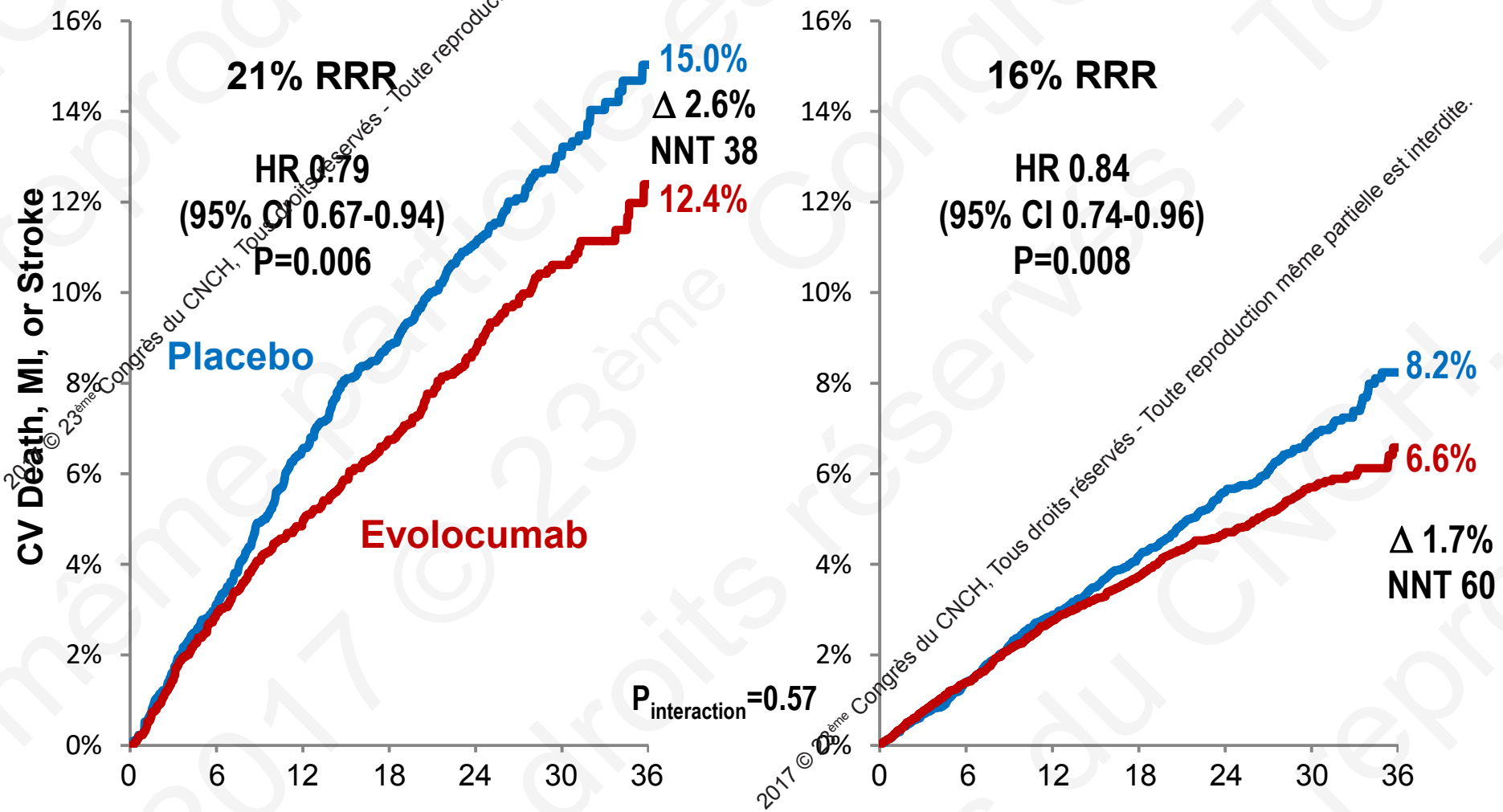
Risk of CV Death, MI or Stroke with Each Risk Factor

Analyses in placebo arm

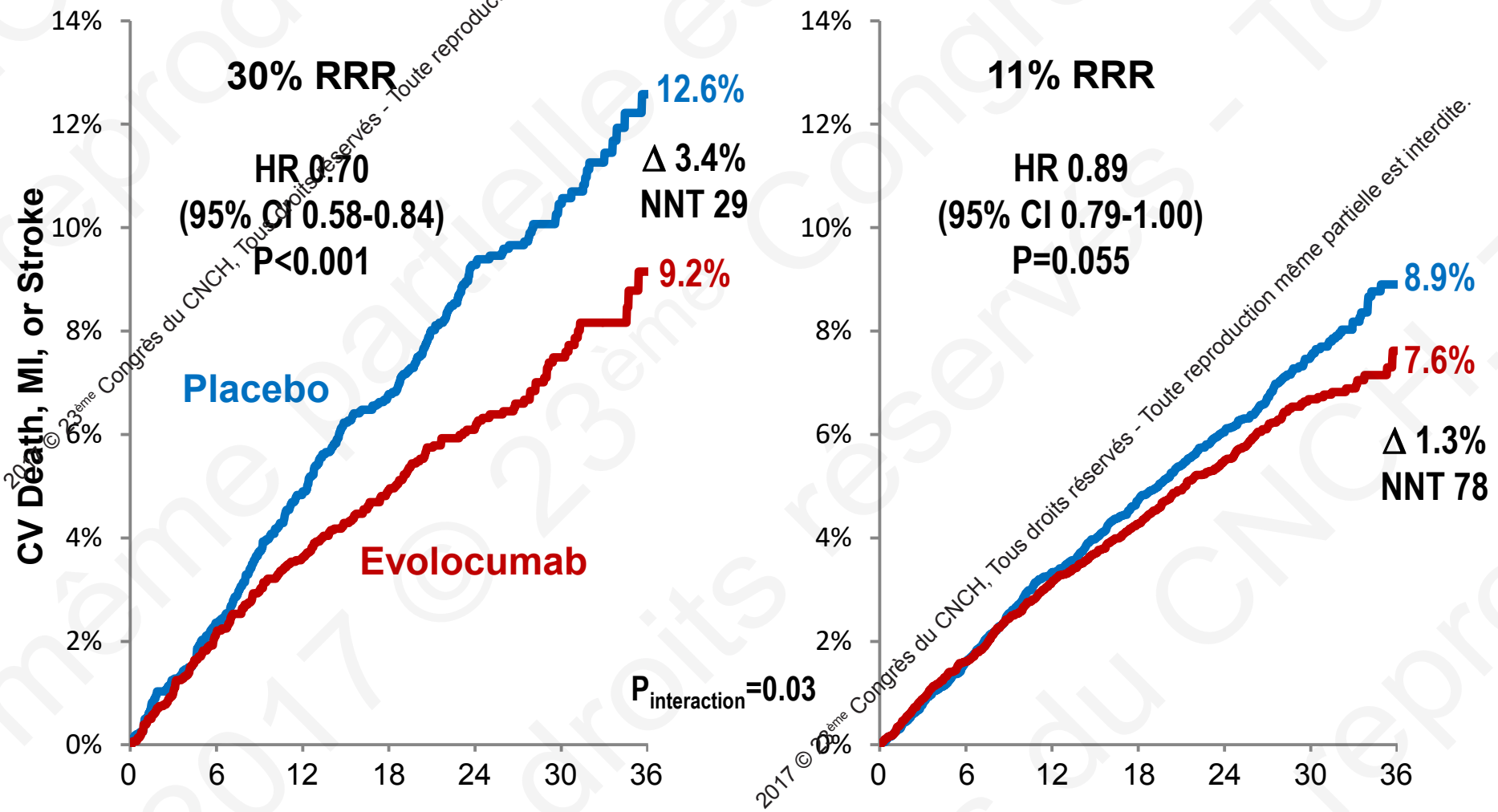
Benefit of EvoMab Based on Time from Qualifying MI



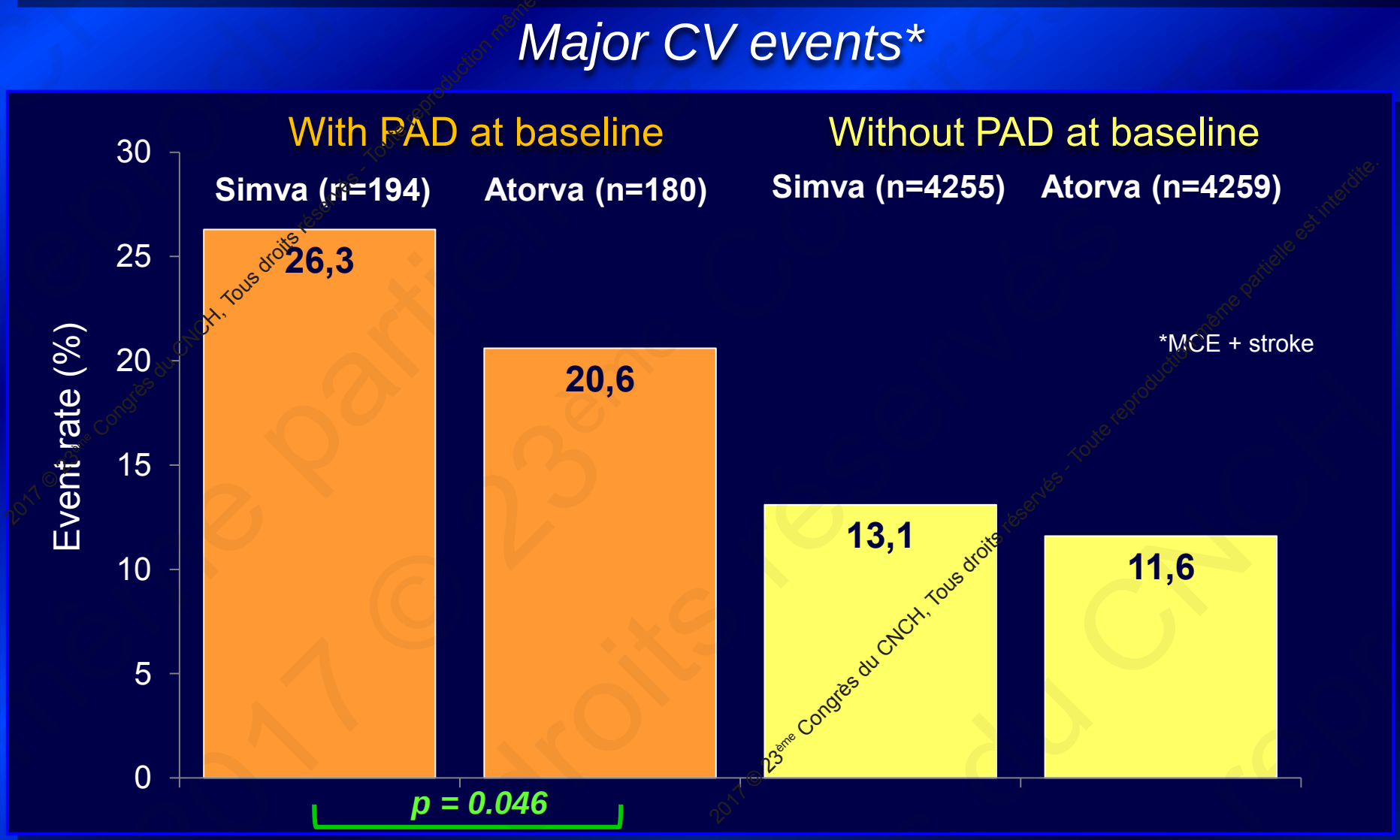
Benefit of EvoMab Based on # of Prior MIs



Benefit of EvoMab Based on Multivessel Disease



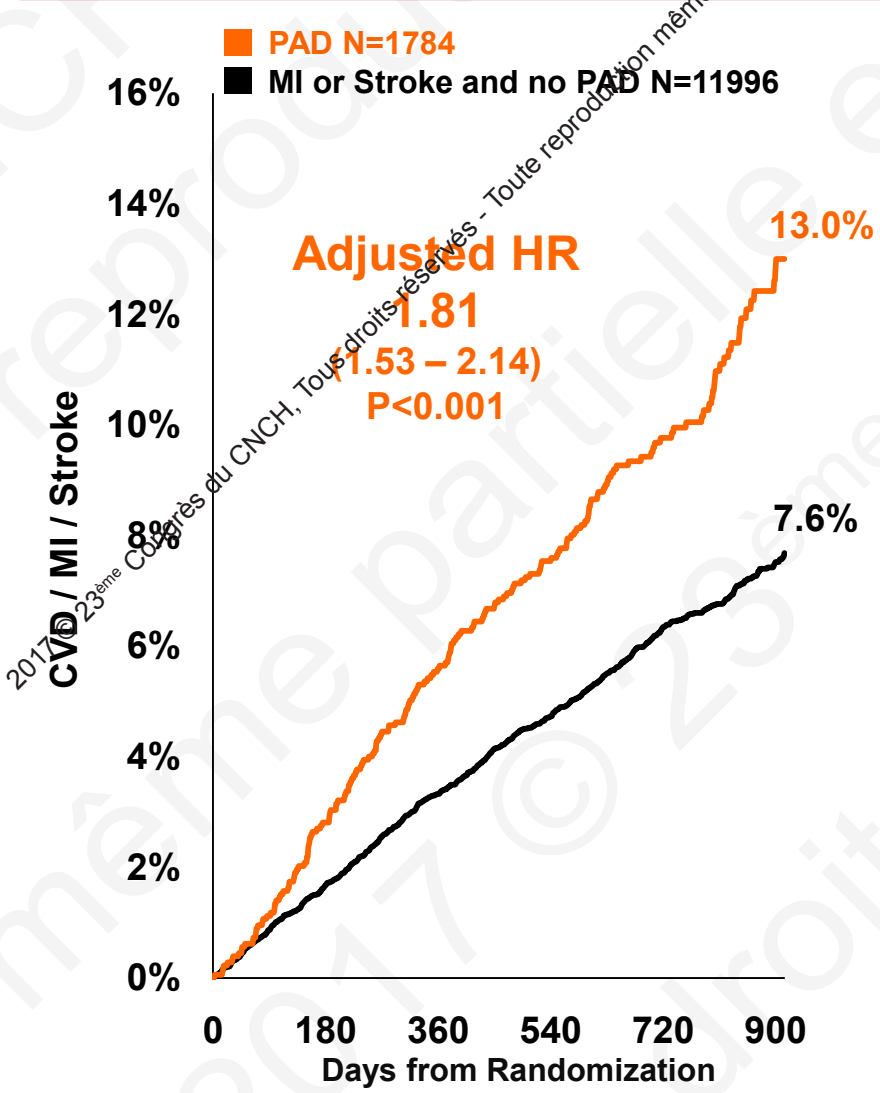
CAD patients with a history of PAD are at higher risk of future CVD events (analysis from IDEAL trial)

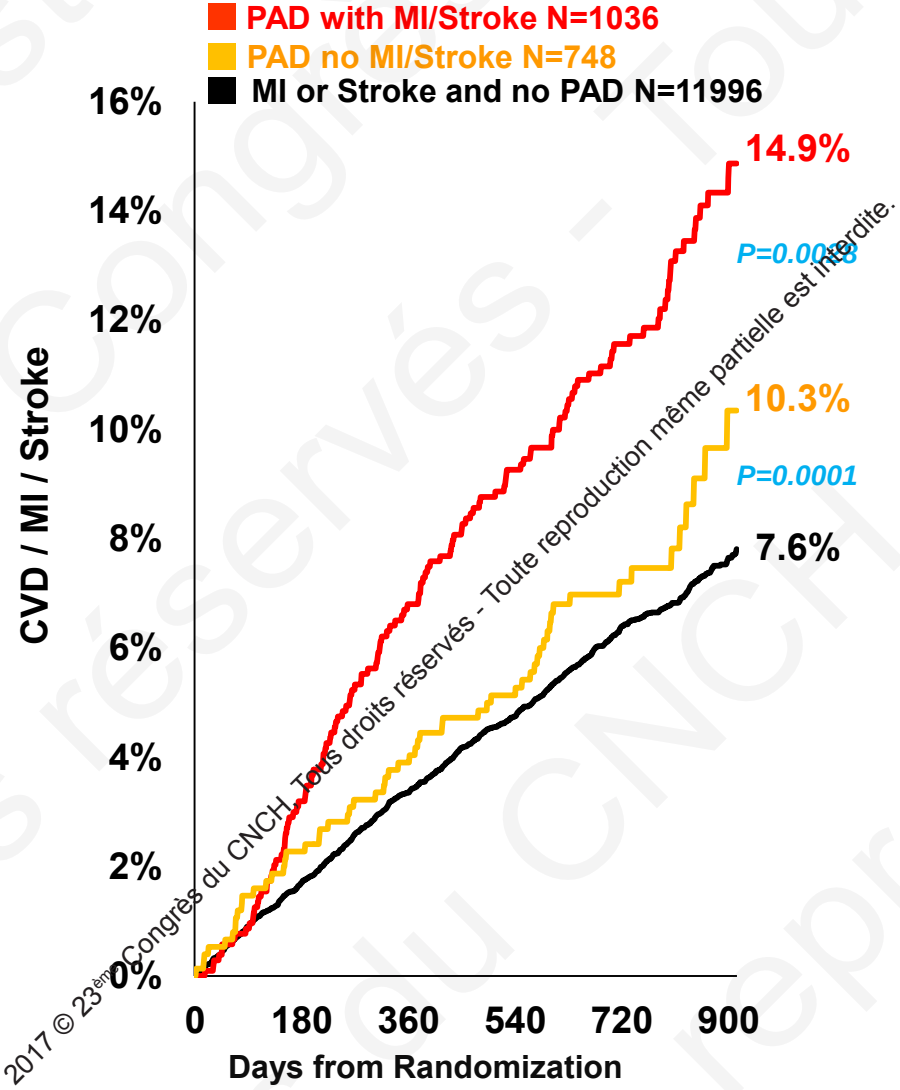


CAD=Coronary Artery Disease; PAD=Peripheral Artery Disease; CVD=Cardiovascular Disease

Stoekenbroek et al. Heart. 2015;101(5):356-62

Peripheral Artery Disease and Risk in Placebo Patients





An Academic Research Organization of
Brigham and Women's Hospital and Harvard Medical School

adjusted age, sex, race, BMI, diabetes, hypertension, smoking, eGFR, CHF, prior MI, CABG/PCI, and history of stroke or TIA.

High Residual Risk for patients with diabetes in secondary prevention

CTT Meta-analysis

(18 686 people with diabetes)

	Major vascular events	
	(control)	*(statin)*
Diabetes	34.9 %	29.6 %
with CHD	RR 0.82	(0.73-0.92)

CTT Collaborators. Lancet 2008; 371:117-125

TNT
TREATING TO NEW TARGETS

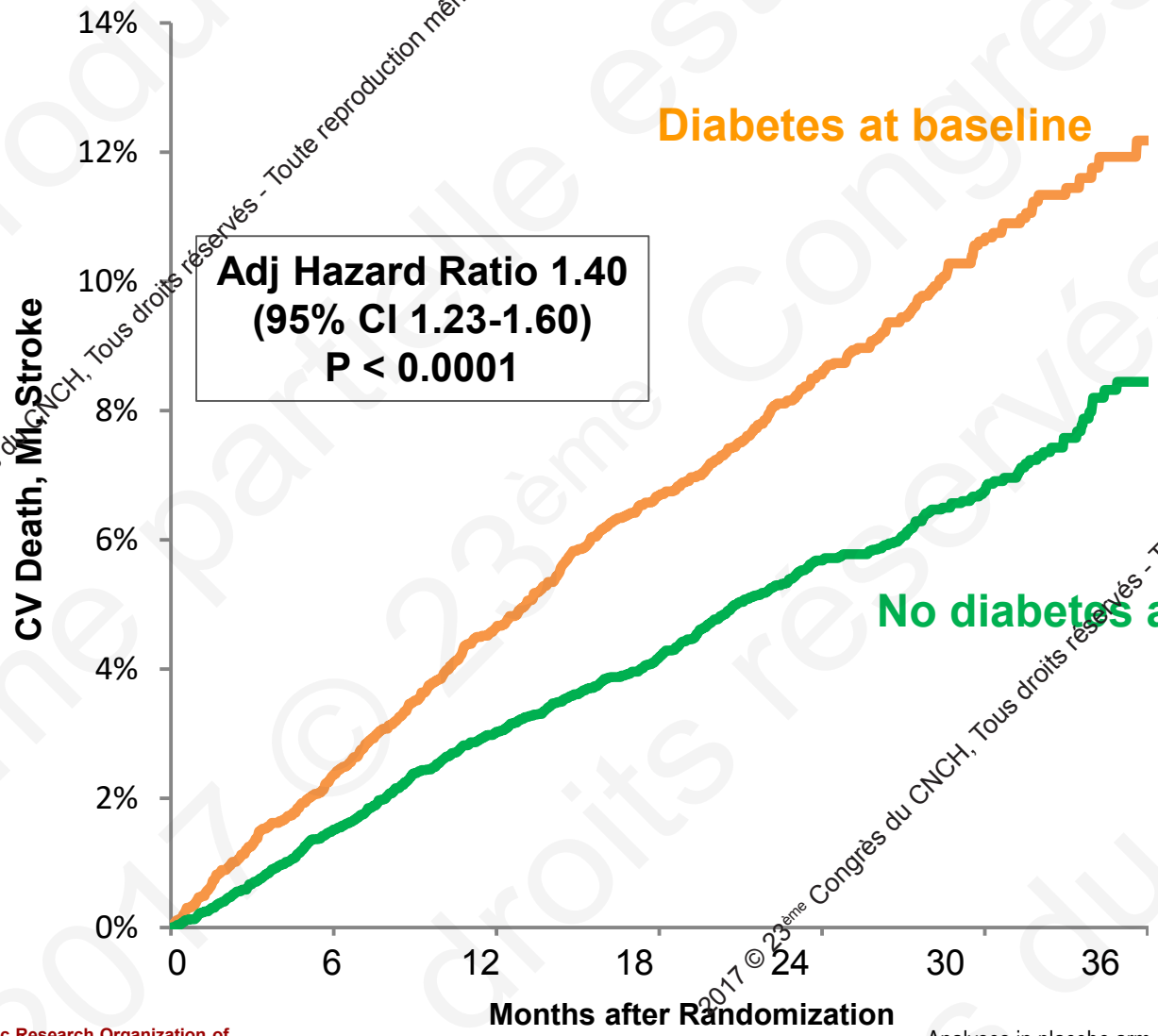
Atorvastatin 80 mg

Diabetes	
Yes	No
39.8 %*	26.1 %*

* CHD, death, nonfatal non–procedure-related MI, resuscitated cardiac arrest, and fatal or nonfatal stroke.

Shepherd et al. Diabetes Care 2006; 29: 1220-6

Risk of Key Secondary Endpoint with Diabetes



Analyses in placebo arm and adj for age, sex, BMI, race, region, history of MI, stroke, PAD, HTN, smoking, HF, eGFR, lipids, statin.

ORIGINAL RESEARCH ARTICLE

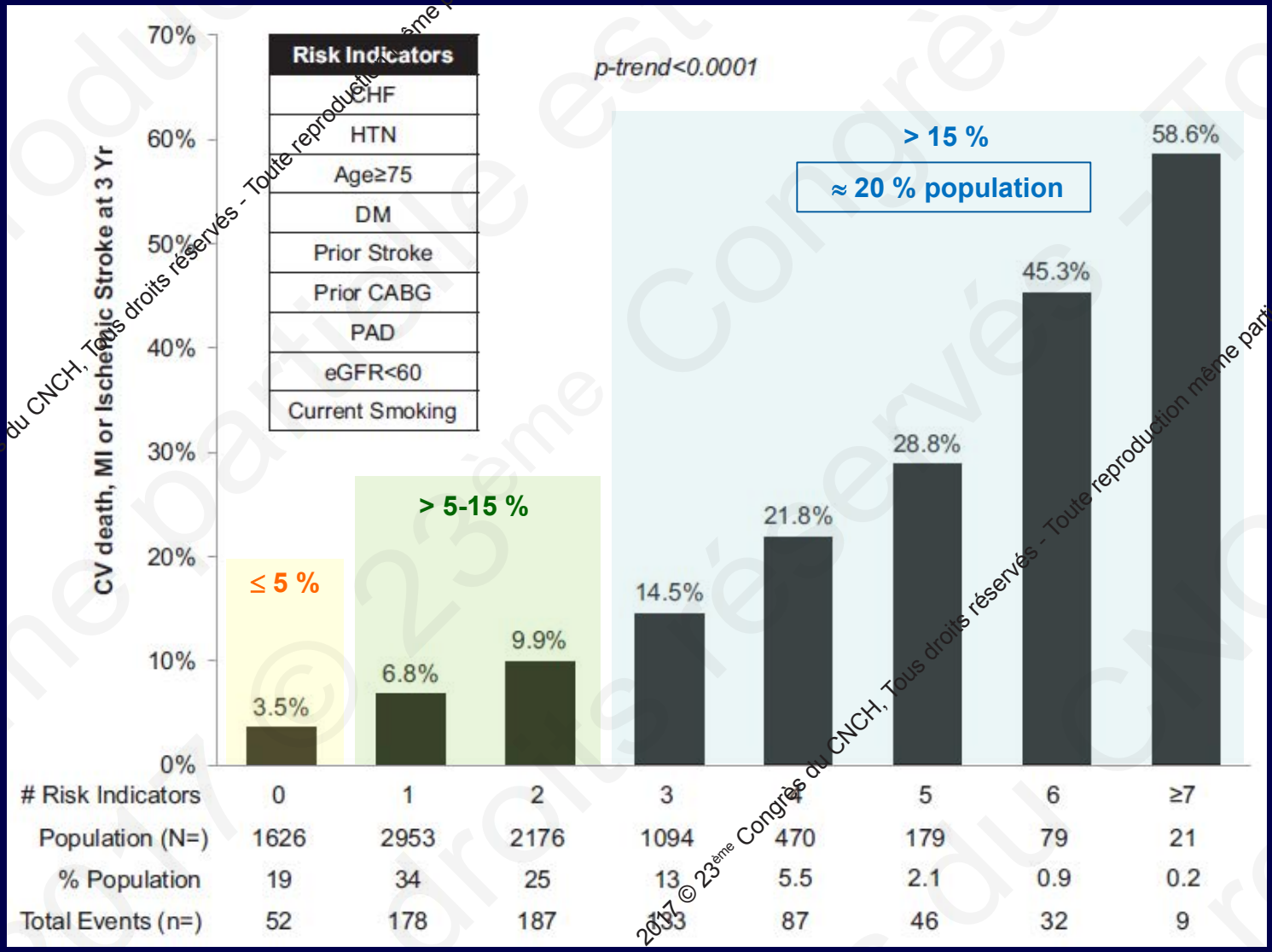
Atherothrombotic Risk Stratification and the Efficacy and Safety of Vorapaxar in Patients With Stable Ischemic Heart Disease and Previous Myocardial Infarction

Risk stratification tool based on 9 independent predictors of recurrent atherothrombosis among placebo-treated patients in the TRA 2°P-TIMI 50 trial.

- age ≥ 75
- diabetes
- hypertension
- smoking
- renal dysfunction
- previous stroke
- previous CABG
- PAD
- CHF

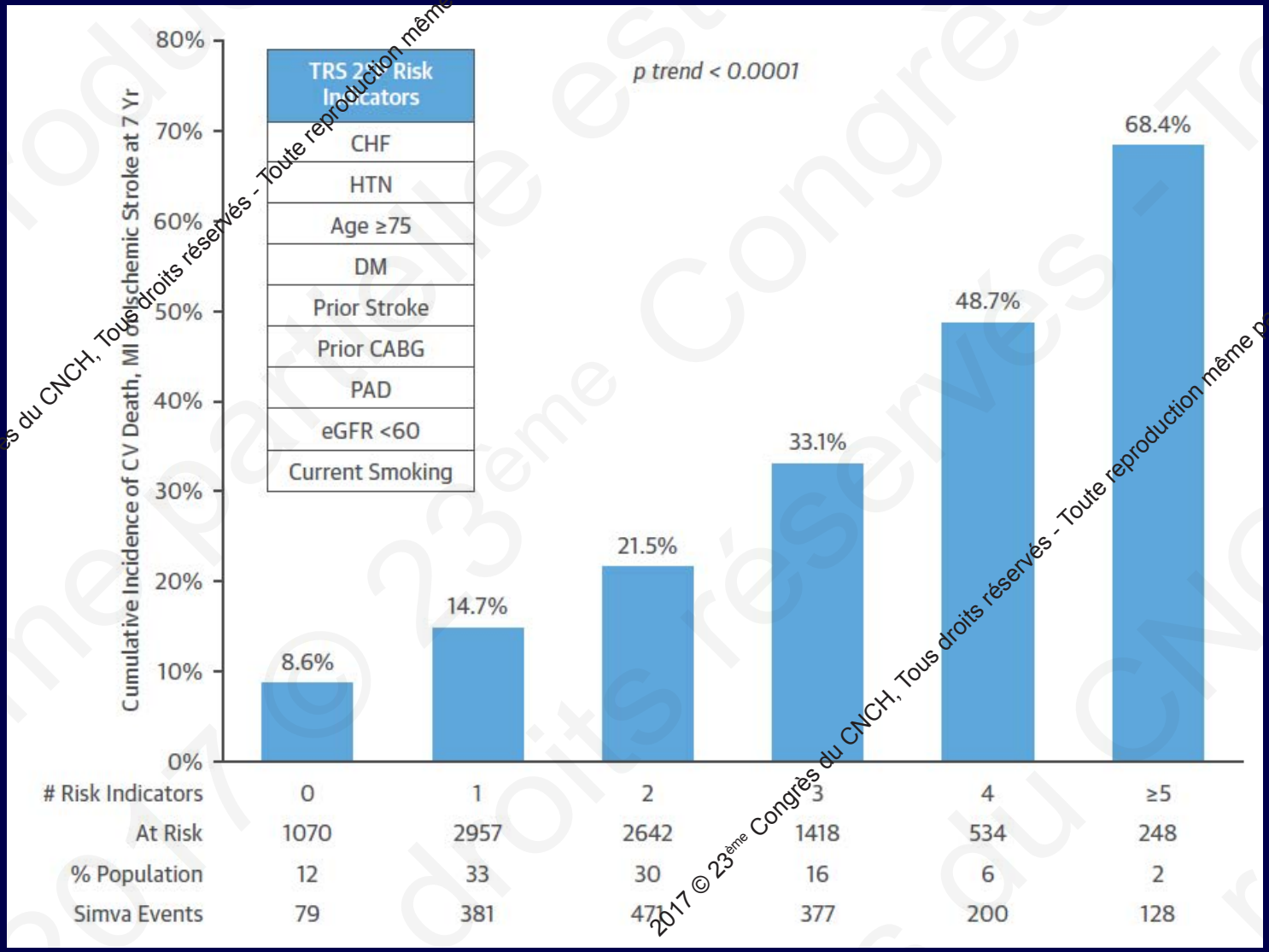
Bohula et al. Circulation 2016; 134: 304-313

Risk stratification of CV death, MI, or ischemic stroke in placebo-treated patients with previous MI (risk at 3-year)



Bohula et al. Circulation 2016; 134: 304-313

IMPROVE-IT : Risk Stratification of CV death, MI, or ischemic stroke in the control arm (placebo/simvastatin)



Bohula et al. J Am Coll Cardiol 2017; 69: 911-21

ORIGINAL RESEARCH ARTICLE

Prognosis of Patients With Familial Hypercholesterolemia After Acute Coronary Syndromes

CONCLUSIONS: Patients with FH and ACS have a >2-fold adjusted risk of coronary event recurrence within the first year after discharge than patients without FH despite the widespread use of high-intensity statins.

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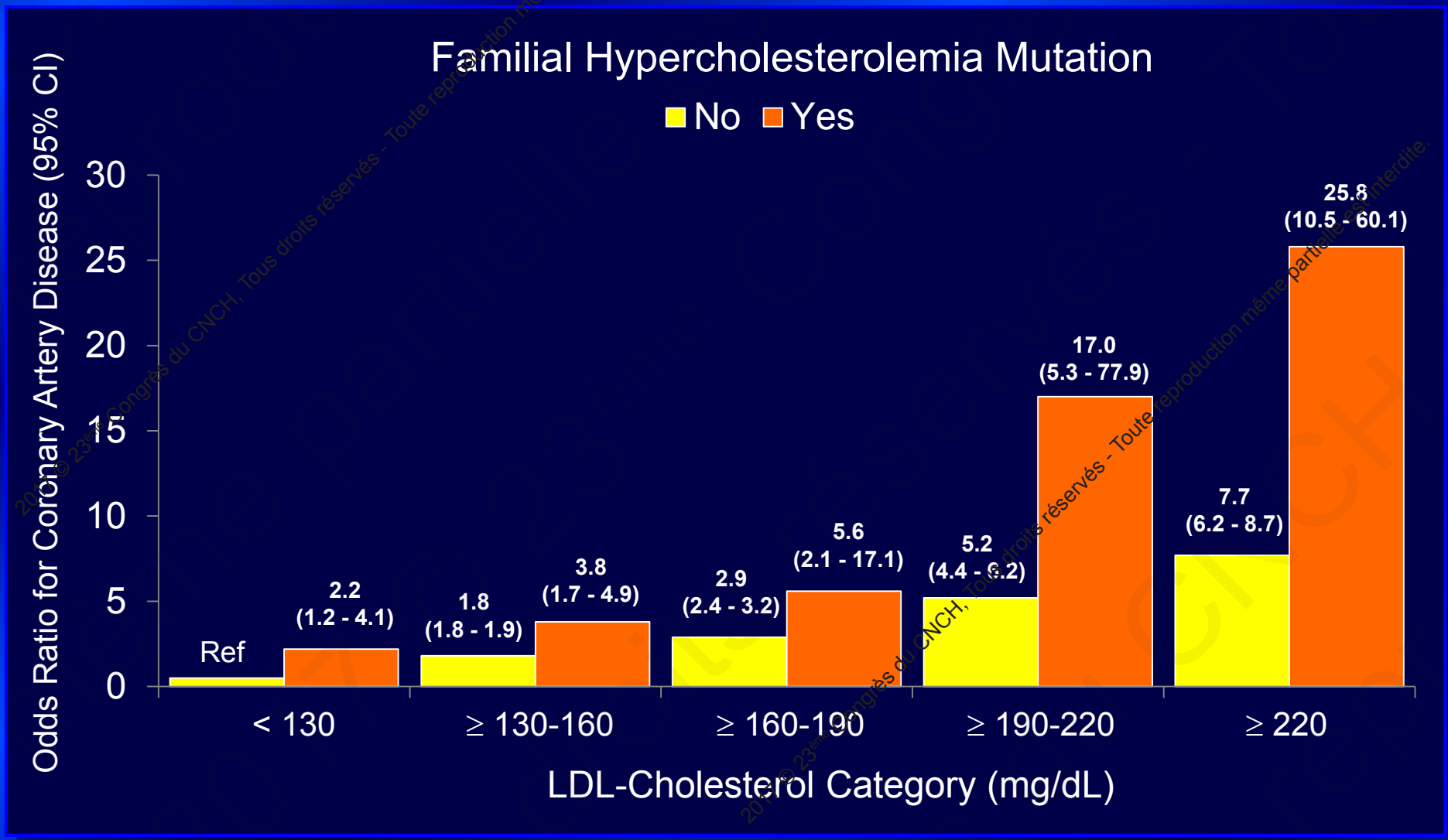
Nanchen et al. Circulation 2016; 134:698-709

For a given observed LDL, FH Mutation Carriers are at Increased Coronary Risk



Khera et al. J Am Coll Cardiol 2016; 67: 2578-89

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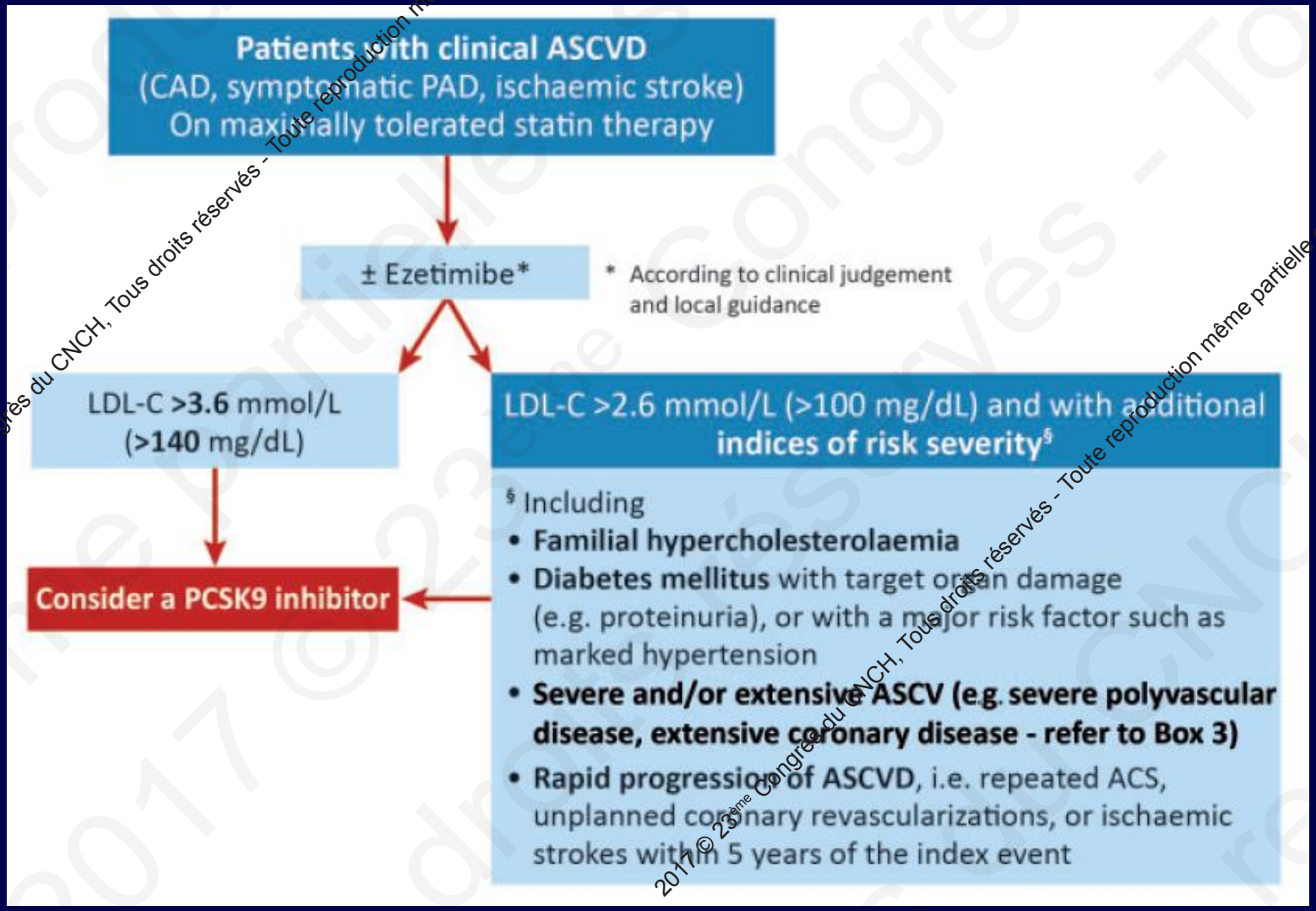
ESC
European Society of Cardiology
European Heart Journal (2017) 0, 1–13
doi:10.1093/eurheartj/ehx549

CURRENT OPINION

2017 Update of ESC/EAS Task Force on practical clinical guidance for proprotein convertase subtilisin/kexin type 9 inhibition in patients with atherosclerotic cardiovascular disease or in familial hypercholesterolaemia

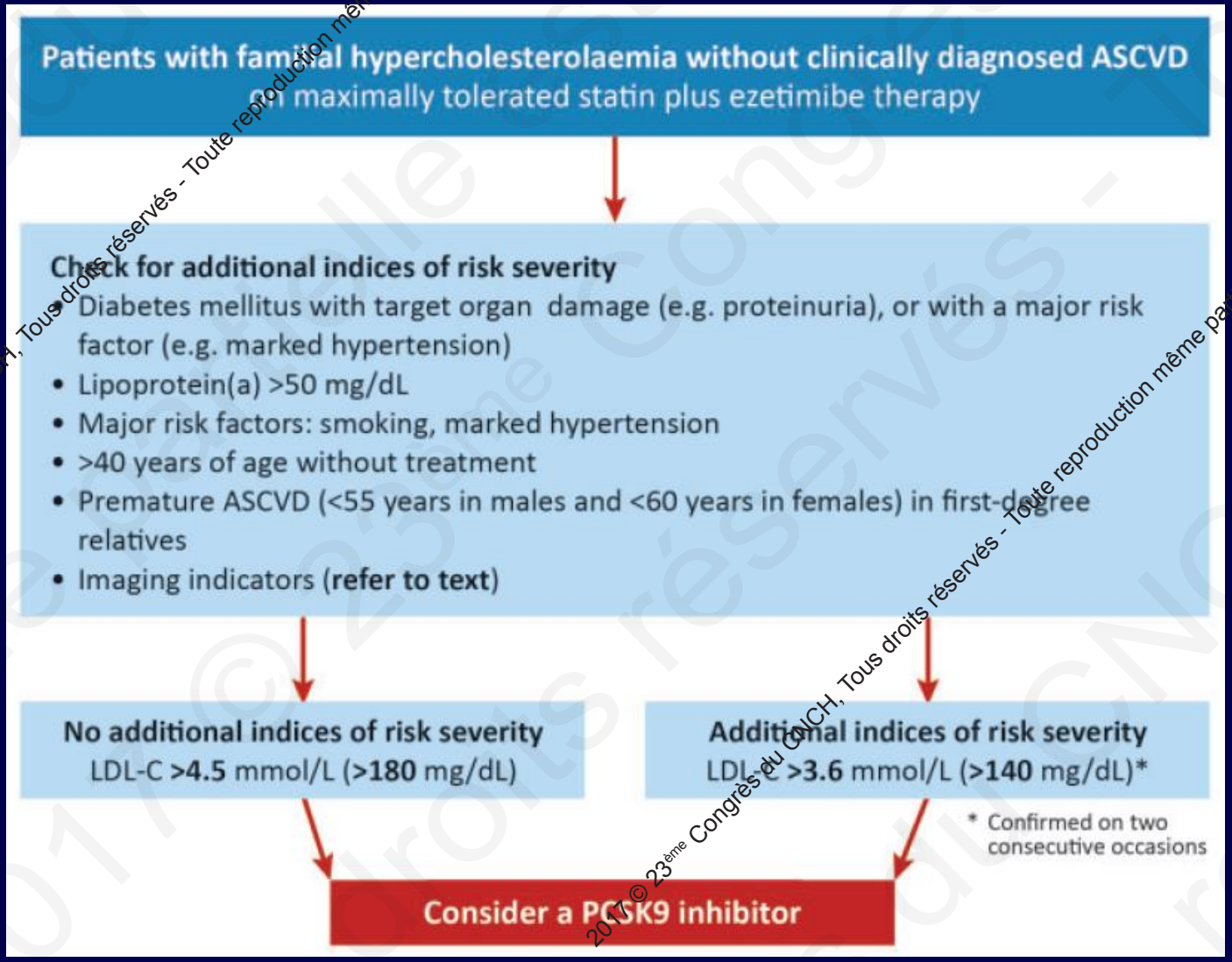
Ulf Landmesser[1]*†, M. John Chapman[2†], Jane K. Stock[3], Pierre Amarenco[4], Jill J.F. Belch[5], Jan Borén[6], Michel Farnier[7], Brian A. Ference[8], Stephan Gielen[9], Ian Graham[10], Diederick E. Grobbee[11], G. Kees Hovingh[12], Thomas F. Lüscher[13], Massimo F. Piepoli[14], Kausik K. Ray[15], Erik S. Stroes[12], Olov Wiklund[16], Stephan Windecker[17], Jose Luis Zamorano[18], Fausto Pinto[19], Lale Tokgözoğlu[20], Jeroen J. Bax[21], and Alberico L. Catapano[22]

Clinical decision algorithm for the use of PCSK9 inhibitors in patients with ASCVD



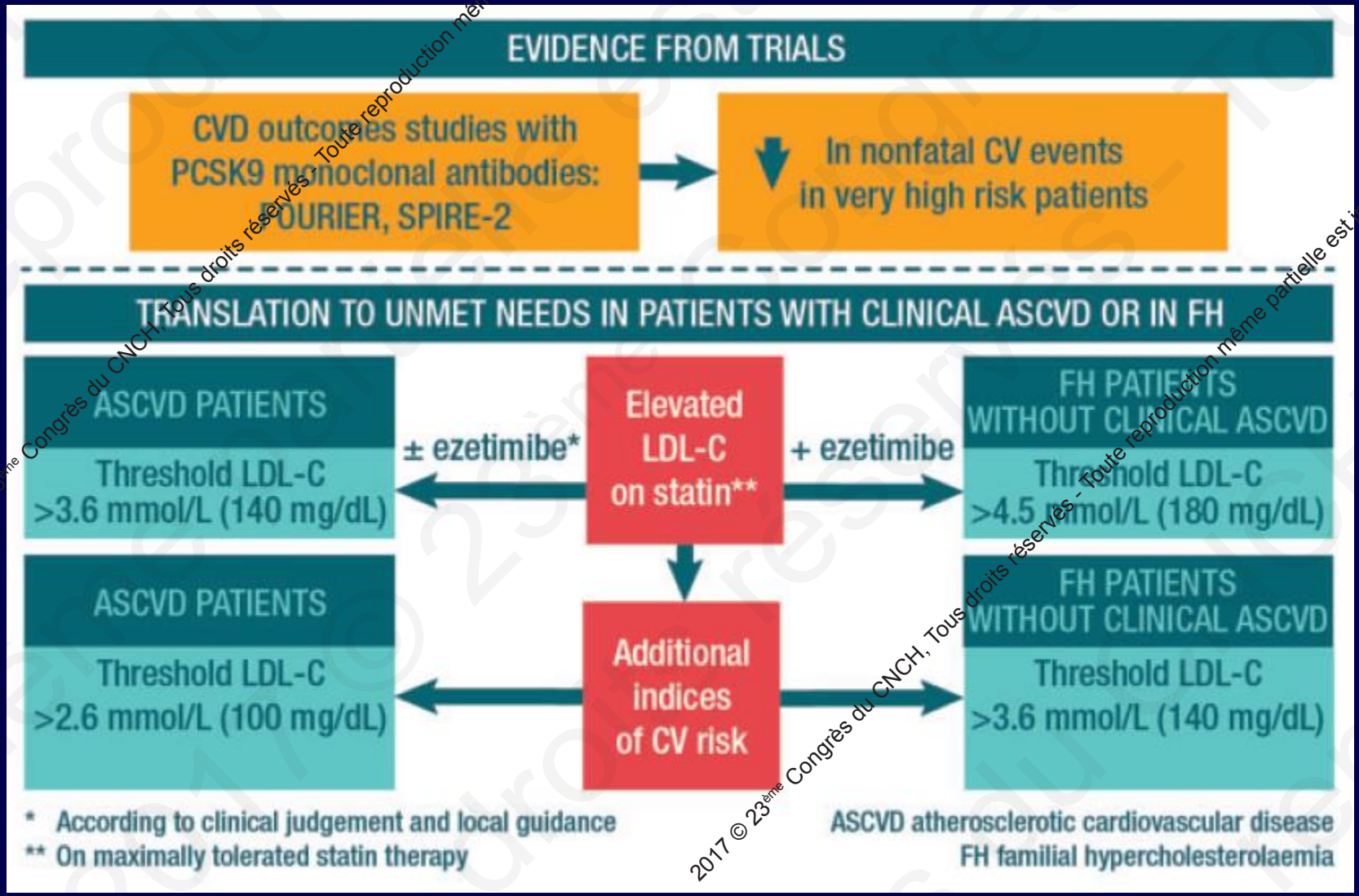
Landmesser et al. Eur Heart J 2017; online

Clinical decision algorithm for the use of a PCSK9 inhibitor in FH patients without clinical ASCVD



Landmesser et al. Eur Heart J 2017; online

Conclusion : In summary



Landmesser et al. Eur Heart J 2017; online