L'Association Tunisienne de Réanimation (ATR)

19ÈME CONGRÈS NATIONAL DE RÉANIMATION

21-23 novembre 2014
à l'hôtel Le Royal - Hammamet

Statines et exacerbations aiguës des broncho-pneumopathies chroniques obstructives.

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Introduction

- **BPCO:**

☞ Maladie **inflammatoire** chronique.

☞ Troisième cause de **mortalité**.

- **Exacerbations fréquentes**: cout élevé, détérioration de la qualité de vie et **augmentation de la mortalité.**
- **Peu de thérapeutiques** ont montré leurs preuves dans la prise en charge ou la **prévention** des EABPCO.

Introduction

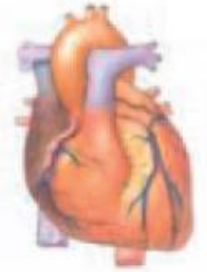
BPCO: Maladie Systémique et Comorbidités fréquentes

Inhaled corticosteroids

Lung inflammation

Statins
ACE inhibitors
PPAR agonists

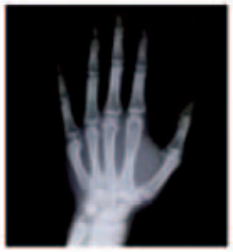
Systemic inflammation



Cardiovascular disease

Skeletal muscle dysfunction

Osteoporosis

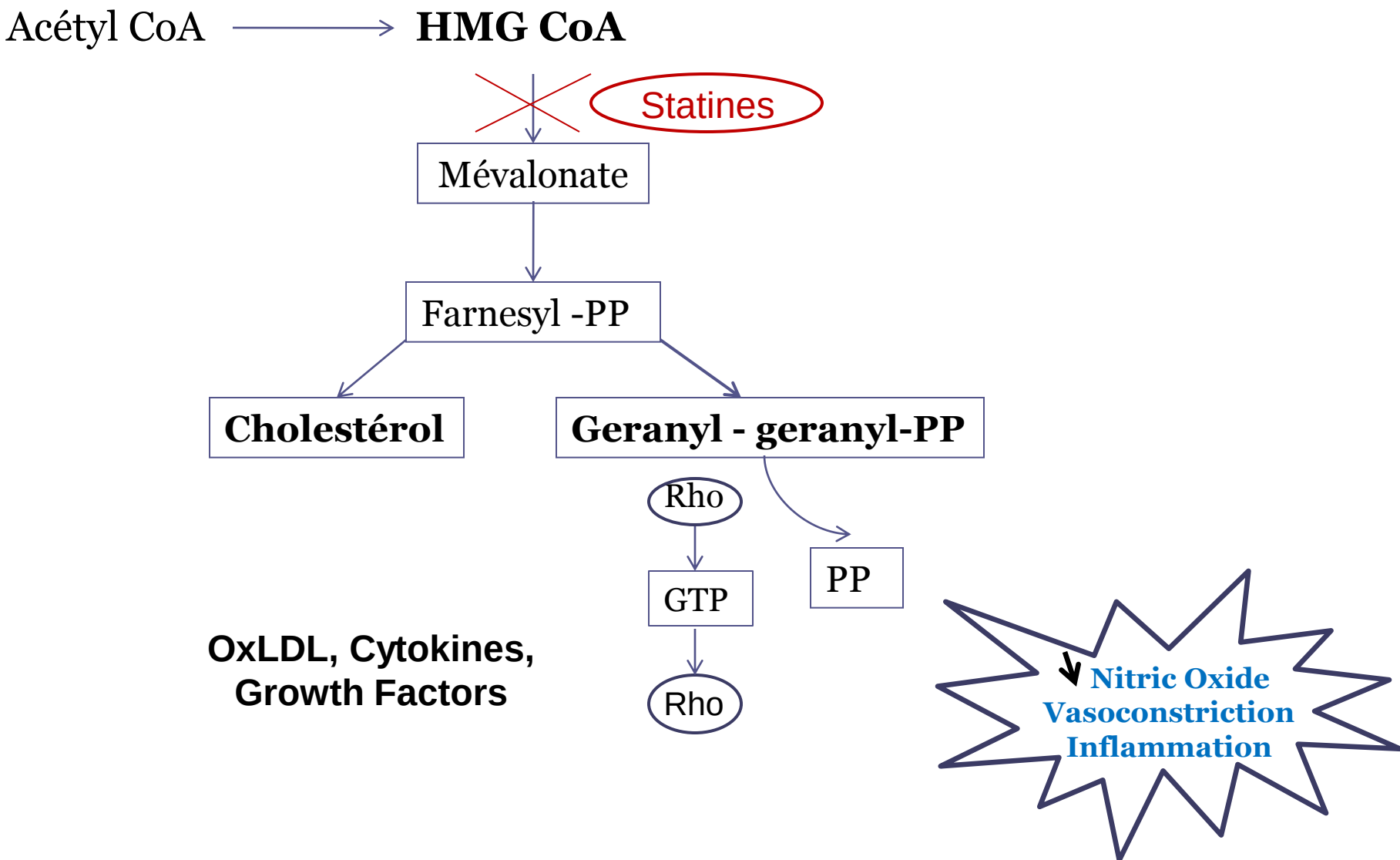


Diabetes

Introduction

- **Statins**: 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors.
- AMM en 1987.
- Améliorent la survie dans la prévention primaire et secondaire de l'athérosclérose (maladie inflammatoire) dans de nombreux RCT.
- **Effets non coronaires +++.**

Introduction



Introduction

Statines = Effets Pléiotropes

- Anti-inflammatoire (↓CRP et cytokines)
- Immunomodulateur
- Amélioration de la fonction endothéliale
- Donneur de NO (↑NOSe, ↓NOSi)
- Anticoagulant
- Antioxydant
- Préservation de la réactivité vasculaire

Mason JC, Clin Sci; 2000; 105: 251-266

Pistes de Recherche Multiples

- Ostéoporose — *Meier CR et al. JAMA 2000*
- Alzheimer — *Jick H et al. Lancet 2000*
- Certains cancers — *Poytner JN et al. NEJM 2005*
- Sclérose en plaque — *Ifergan I et al. Ann Neurol 2006*
- Polyarthrite rhumatoïde — *McCarey DW. Lancet 2004*

Autres…

En Réanimation

- Sepsis sévère et choc septique.
- Chirurgie cardiaque et vasculaire
- SDRA
- BPCO

Mekontso Dessap *et al. Critical Care* 2011, **15**:R171
http://ccforum.com/content/15/4/R171

Statines et Sepsis

CRITICAL CARE

RESEARCH Open Access

Effects of discontinuing or continuing ongoing statin therapy in severe sepsis and septic shock: a retrospective cohort study

Armand Mekontso Dessap[1,2,3*†], Islem Ouanes[1,4†], Nerlep Rana[1], Beatrice Borghi[1], Christophe Bazin[5], Sandrine Katsahian[6], Anne Hulin[5] and Christian Brun-Buisson[1,2,3]

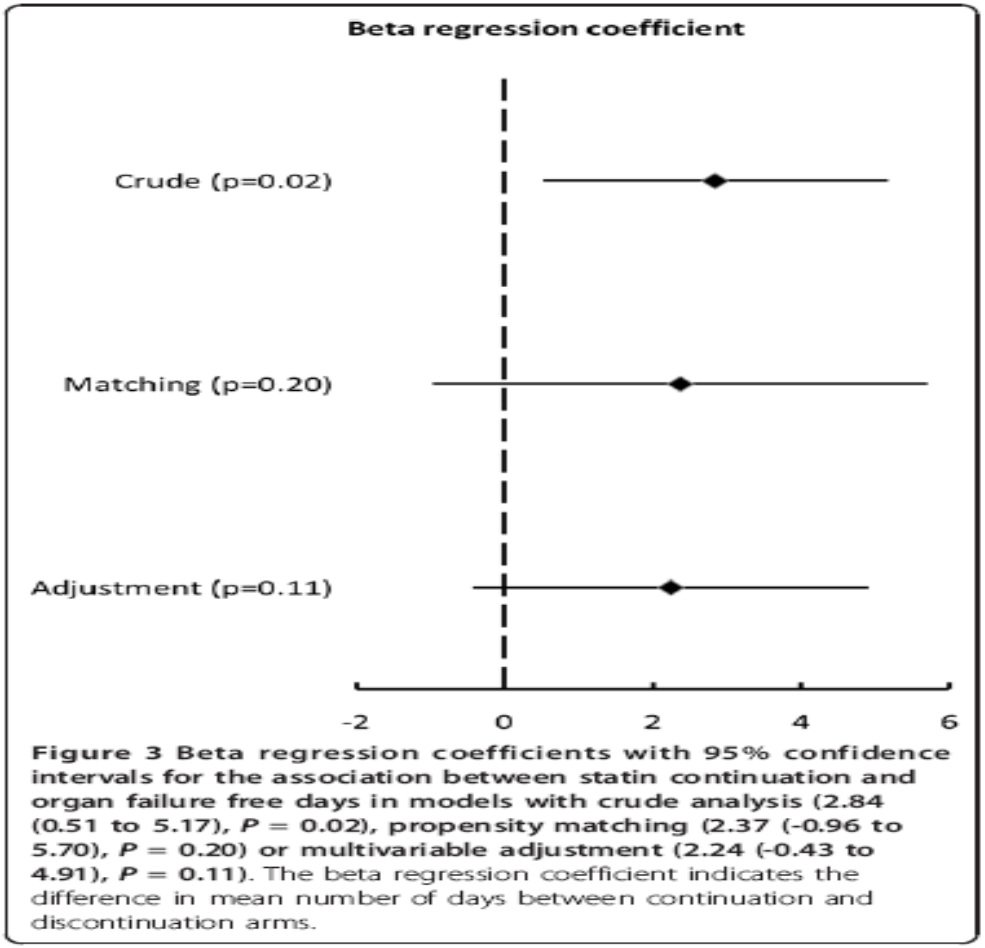


Figure 3 Beta regression coefficients with 95% confidence intervals for the association between statin continuation and organ failure free days in models with crude analysis (2.84 (0.51 to 5.17), *P* = 0.02), propensity matching (2.37 (-0.96 to 5.70), *P* = 0.20) or multivariable adjustment (2.24 (-0.43 to 4.91), *P* = 0.11). The beta regression coefficient indicates the difference in mean number of days between continuation and discontinuation arms.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rosuvastatin for Sepsis-Associated Acute Respiratory Distress Syndrome

Statines et SDRA

The National Heart, Lung, and Blood Institute
ARDS Clinical Trials Network*

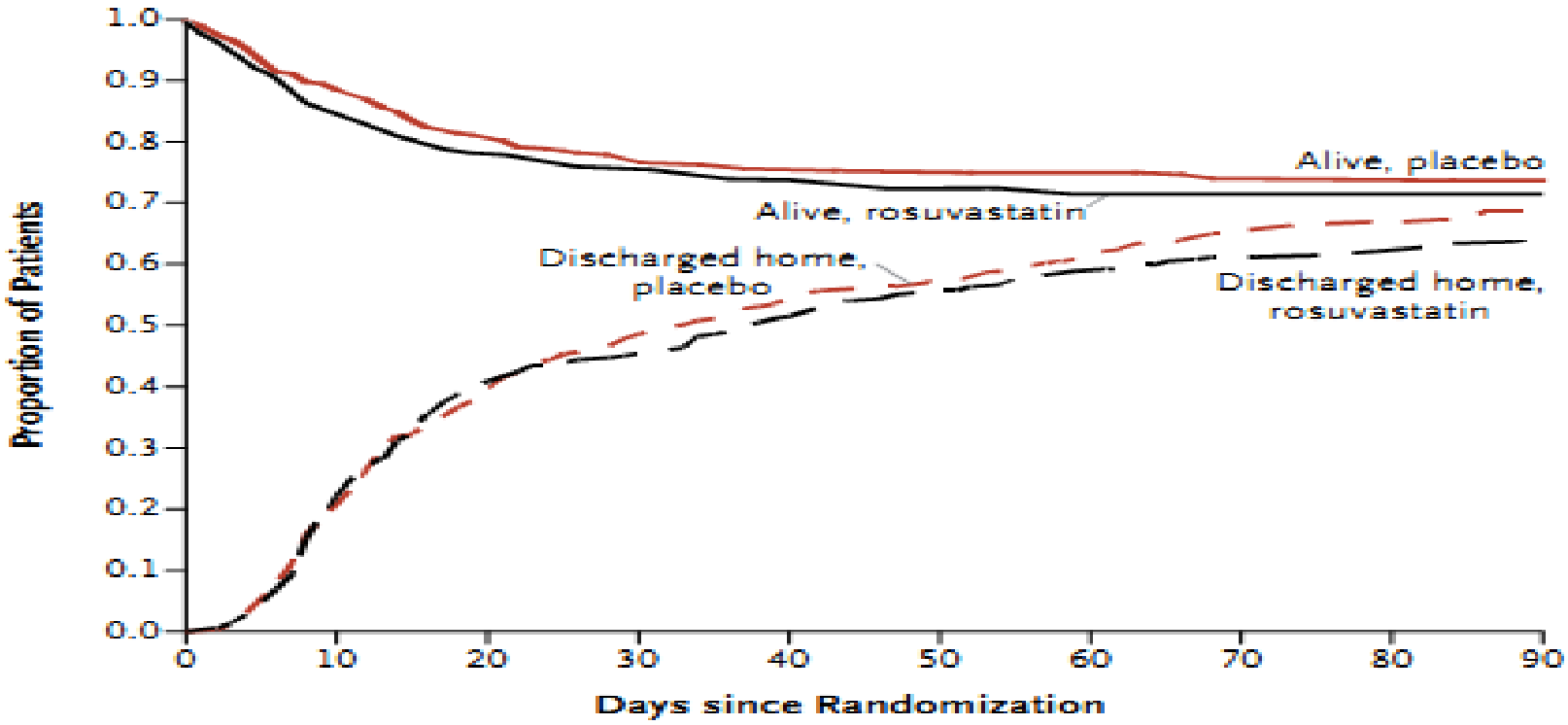


Figure 2. Probability of Survival and of Being Discharged Home during the First 90 Days after Randomization.

Statines et BPCO

- Prévention des EABPCO +++
- Fonction respiratoire
- Mortalité par EABPCO
- Pas de place actuelle dans le traitement de l'exacerbation

Statines et BPCO
Etudes Observationnelles

Statines et BPCO

- **Plusieurs études:** les statines pourraient avoir un bénéfice chez les BPCO:
- *Observationnelles*
- *Rétrospectives*
- **Bénéfices rapportés:**
- Réduction de la fréquence et de la sévérité des EABPCO
- Ralentissement du déclin de la fonction respiratoire
- Réduction du recours à la VM,
- Réduction de la mortalité des BPCO.

Eur Respir J 2007; 29: 279–283
DOI: 10.1183/09031936.00106406

Statin use is associated with reduced mortality in COPD

V. Søyseth, P.H. Brekke, P. Smith and T. Omland

Lørenskog, Norway.

- Cohorte **Rétrospective** (2000-2003).
- **854 BPCO** consécutifs à la **sortie après exacerbation** (âge moyen: 70,8 ans, 51,5% de femmes).
- **118 patients sous statines** à la sortie de l'hôpital
- **333 décès pour un suivi moyen** de 1,9 ans.
- **Mortalité Brute**: - Statines: 110/1000personnes.an.

  - Sans statines: 191/1000 personnes.an.

Eur Respir J 2007; 29: 279–283
DOI: 10.1183/09031936.00106406

Statin use is associated with reduced mortality in COPD

TABLE 3 Multivariate Cox regression analyses of mortality after discharge from the hospital

Covariate	HR (95% CI)	p-value
Sex[#]	0.89 (0.70–1.2)	0.4
Age yrs		
<60	1	
60–69	1.6 (0.93–2.8)	0.09
70–79	2.5 (1.5–4.1)	<0.001
⩾80	4.5 (2.7–7.6)	<0.001
Current smoking[¶]	1.2 (0.89–1.7)	0.2
FEV_1 % pred+10%	0.80 (0.74–0.86)	<0.001
Comorbidity[+]		
Ischaemic heart disease	1.3 (1.0–1.7)	0.03
Congestive heart failure	1.6 (1.2–2.2)	0.001
Atrial fibrillation	1.6 (1.2–2.1)	0.002
Diabetes	1.8 (1.3–2.5)	<0.001
Venous thromboembolism	2.0 (1.0–3.7)	0.04
Lung cancer	4.6 (2.8–7.5)	<0.001
Cancer other sites	2.3 (1.6–3.3)	<0.001
Treatment		
Statins	0.57 (0.38–0.87)	0.009
Inhaled corticosteroids	0.73 (0.57–0.94)	0.01

-Statines seules: HR=0,69

-Corticoïdes inhalés seuls: HR=0,75

-Statines+ Corticoïdes inhalés: HR=0,39

Le traitement par les statines était associé à une augmentation de la survie après une EABPCO

CHEST

Original Research

NOVEL PHARMACOTHERAPY

Influenza and COPD Mortality Protection as Pleiotropic, Dose-Dependent Effects of Statins*

Floyd J. Frost, PhD; Hans Petersen, MS; Kristine Tollestrup, PhD; and Betty Skipper, PhD

- Matched cohort study (76232 patients).

(CHEST 2007; 131:1006–1012)

Table 1—*Characteristics of Patients in the Matched Cohort Study

Characteristics	Statin Use (n = 19,058)		No Statin Use
	Low Daily Dose	Moderate Daily Dose	
Cohort	7,475 (39.2)	11,583 (60.8)	57,174
Born 1946 to 1955	2,272 (30.4)	2,806 (24.2)	15,234 (26.6)
Born 1921 to 1945	4,746 (63.5)	8,054 (69.5)	38,400 (67.2)
Born in 1920 or before	457 (6.1)	723 (6.2)	3,540 (6.2)
Male	3,637 (48.7)	6,292 (54.3)	29,787 (52.1)
Female	3,838 (51.3)	5,291 (45.7)	27,387 (47.9)
Mean No. of medications prior to statin use	7,475 (9.5†)	11,583 (8.4†)	57,174 (6.2†)
CCI score ≥ 2 during phase 1	7,475 (10.7)	11,583 (12.1)	57,174 (5.6)
Three or more influenza vaccinations in phase 2	7,475 (2.2)	11,583 (4.1)	57,174 (1.9)
Pneumonia or influenza (ICD-9-CM 480–487) deaths	11 (0.12)	18 (0.14)	94 (0.15)
Unspecified pneumonia and influenza (ICD-9-CM 486–487) deaths	8 (0.13)	16 (0.12)	80 (0.13)
COPD (ICD-9-CM 490–496) deaths	8 (0.09)	5 (0.04)	84 (0.14)

CHEST

Original Research

NOVEL PHARMACOTHERAPY

Influenza and COPD Mortality Protection as Pleiotropic, Dose-Dependent Effects of Statins*

Floyd J. Frost, PhD; Hans Petersen, MS; Kristine Tollestrup, PhD; and Betty Skipper, PhD

(CHEST 2007; 131:1006–1012)

- 397 Décès par la grippe et 207 Décès par BPCO.
- Les statines même à dose faible (≥4 mg/j), réduisent significativement le risque de décès par **grippe/pneumonie (OR=0,60)** et par **EABPCO (OR=0,17).**

Tohoku J. Exp. Med., 2007, **212**, 265-273

Decrease in Mortality Rate of Chronic Obstructive Pulmonary Disease (COPD) with Statin Use: A Population-Based Analysis in Japan

WATARU ISHIDA,[1] TAKASHI KAJIWARA,[1] MOTOTSUGU ISHII,[1] FUMIKADO FUJIWARA,[1] HARUHITO TANEICHI,[1] NORIKO TAKEBE,[1] KAZUMA TAKAHASHI,[1] YOSHIHITO KANEKO,[1] IKUO SEGAWA,[2] HIROSHI INOUE[3] and JO SATOH[1]

[1]Department of Diabetes and Metabolism, Iwate Medical University, Morioka, Japan
[2]Second Department of Internal Medicine, Iwate Medical University, Morioka, Japan
[3]Third Department of Internal Medicine, Iwate Medical University, Morioka, Japan

Horita *et al. Respiratory Research* 2014, **15**:80
http://respiratory-research.com/content/15/1/80

RESPIRATORY RESEARCH

RESEARCH Open Access

Statins reduce all-cause mortality in chronic obstructive pulmonary disease: a systematic review and meta-analysis of observational studies

Nobuyuki Horita[1,2*], Naoki Miyazawa[2], Ryota Kojima[2], Miyo Inoue[2], Yoshiaki Ishigatsubo[1], Atsuhisa Ueda[1] and Takeshi Kaneko[3]

Table 1 Summary of included studies

Author, Year	Design	Quality	Observed patients		Mortality	HR (95% CI)
			recruitment	no		
Søyseth '07 [10]	Retro	7	Post exacerbation	854	All	0.57 (0.38-0.87)
Gestel '08 [11]	Pro	8	Post arterial surgery	1310	All	0.67 (0.52-0.86)
Gestel '09 [12]					Cancer	0.57 (0.32-1.01)
Rutten '10 [13]	Retro	6	Population based	2230	All	0.83 (0.65-1.08)
Short '11 [14]	Retro	6	Post COPD admission	5977	All	0.89 (0.81-0.97)
Bartziokas '11 [15]	Pro	8	Post exacerbation	245	All	0.85 (0.27-2.69)
Lawes '12 [16]	Retro	7	Post COPD admission	1687	All	0.69 (0.58-0.84)
Young '13 [16,17]	Retro	7	Post COPD admission	1687	Resp	0.55 (0.43-0.78)
Sheng '12 [18]	Retro	7	Population based Primary prevention	1274	All	0.61 (0.43-0.85)
					CV	0.90 (0.35-2.34)
Sheng '12 [18]	Retro	7	Population based Secondary prevention	443	All	0.58 (0.35-0.97)
					CV	0.32 (0.13-0.77)
Ekström '13 [19]	Pro	6	Population based On long-term oxygen therapy	2249	All	0.86 (0.72-1.03)

Horita *et al. Respiratory Research* 2014, **15**:80
http://respiratory-research.com/content/15/1/80

RESPIRATORY RESEARCH

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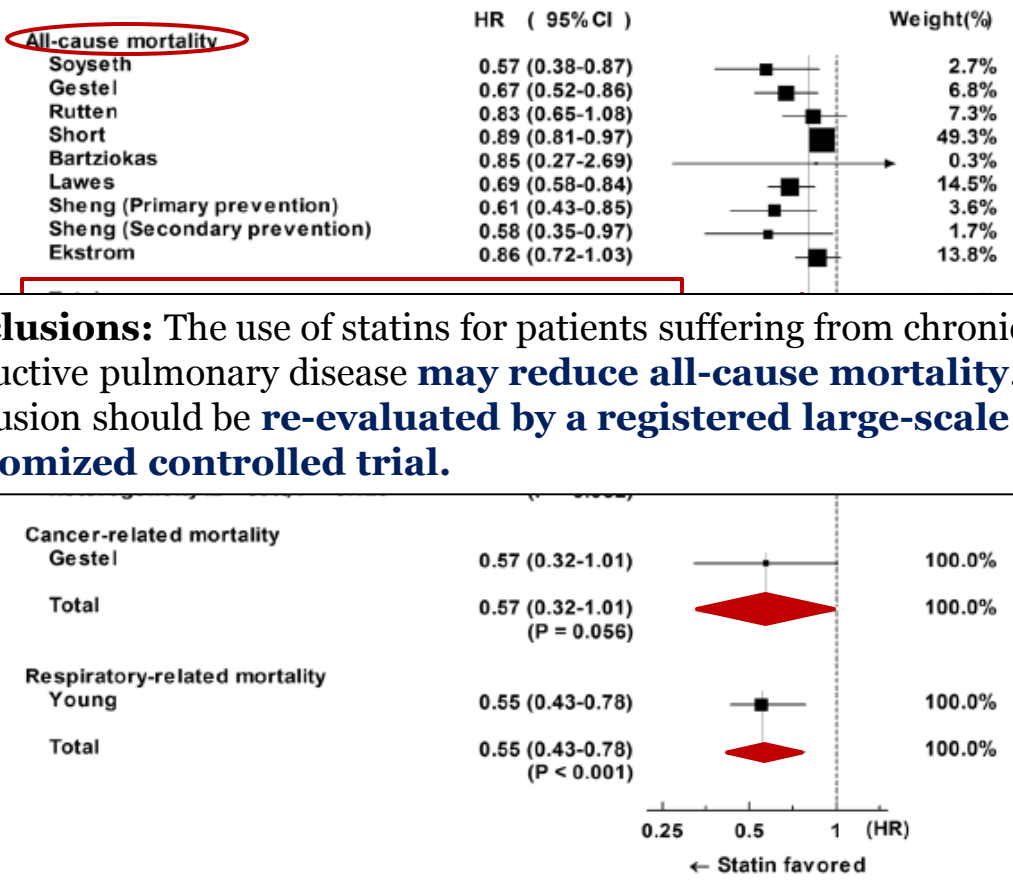
Statins reduce all-cause mortality in chronic obstructive pulmonary disease: a systematic review and meta-analysis of observational studies



Conclusions: The use of statins for patients suffering from chronic obstructive pulmonary disease **may reduce all-cause mortality**. This conclusion should be **re-evaluated by a registered large-scale randomized controlled trial.**

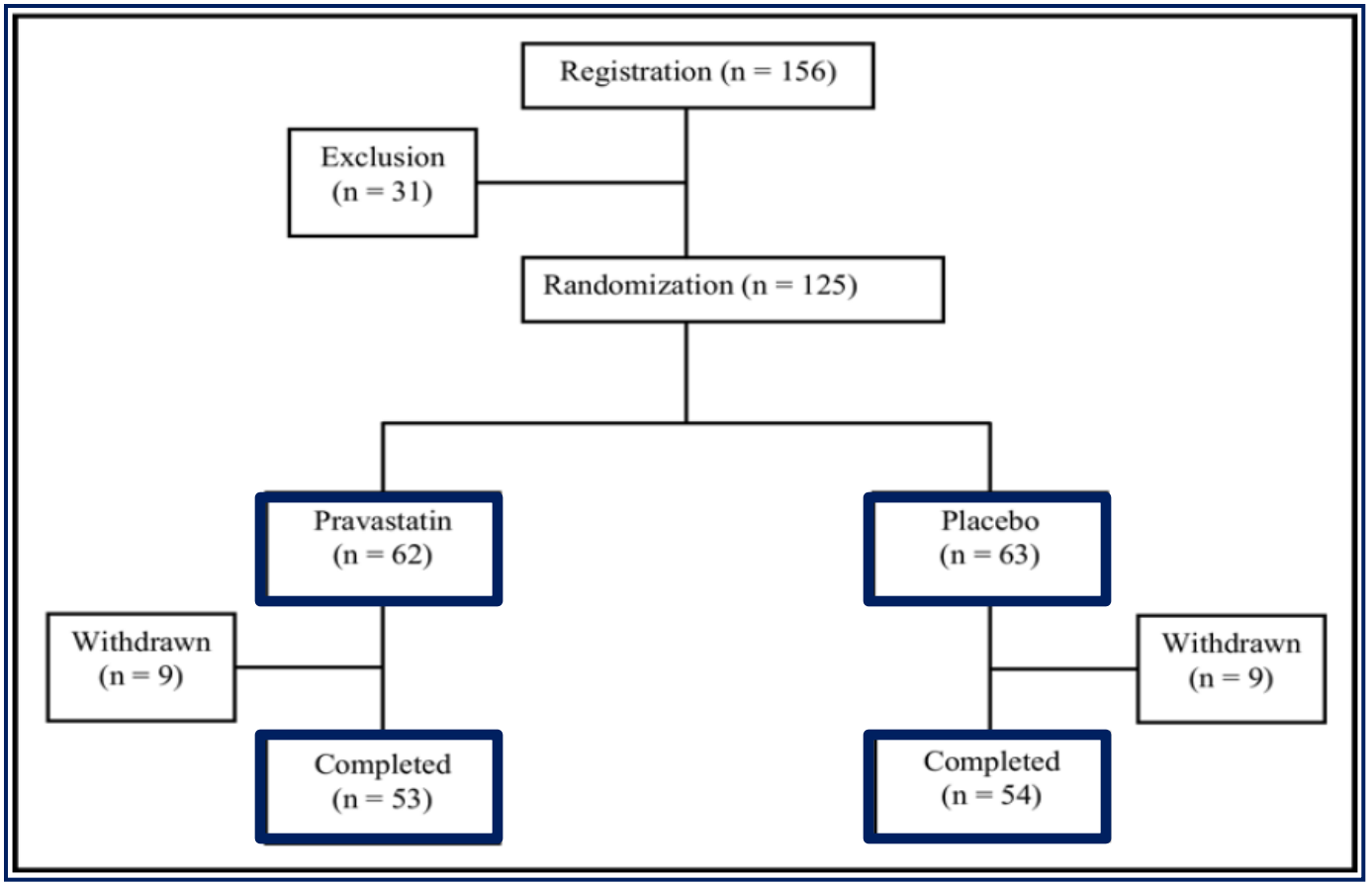
Figure 2 Forest plots for hazard ratio (HR) of statins for mortality.

Statines et BPCO
Etudes randomisées prospectives?

Usefulness of C-Reactive Protein and Interleukin-6 as Predictors of Outcomes in Patients With Chronic Obstructive Pulmonary Disease Receiving *Pravastatin*

Tsung-Ming Lee, MD[a], Mei-Shu Lin, PhD[b], and Nen-Chung Chang, MD, PhD[c,*]

(Am J Cardiol 2008;101:530–535)



Usefulness of C-Reactive Protein and Interleukin-6 as Predictors of Outcomes in Patients With Chronic Obstructive Pulmonary Disease Receiving *Pravastatin*

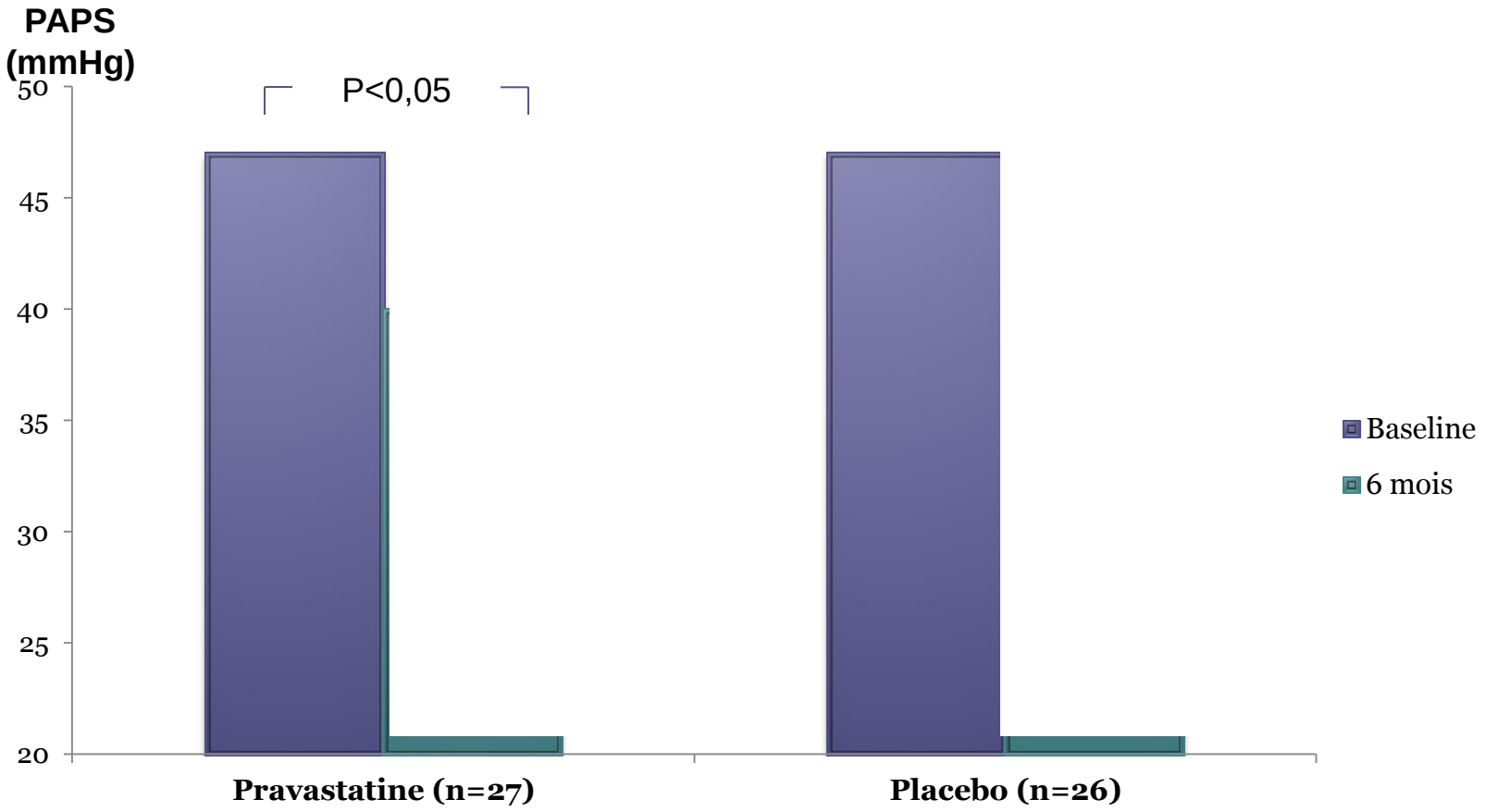
Tsung-Ming Lee, MD[a], Mei-Shu Lin, PhD[b], and Nen-Chung Chang, MD, PhD[c,*]

(Am J Cardiol 2008;101:530–535)

Hemodynamics, biochemistry, and hemoglobin at baseline and after six months of therapy

Parameters	Pravastatin		Placebo	
	Baseline (n = 62)	Follow-up (n = 53)	Baseline (n = 63)	Follow-up (n = 54)
Blood pressure (mm Hg)				
Systolic	135 ± 14	131 ± 16	134 ± 14	131 ± 16
Diastolic	78 ± 10	80 ± 8	76 ± 9	80 ± 8
Pulse pressure	56 ± 12	52 ± 14	58 ± 12	52 ± 14
Heart rate (beats/min)	89 ± 14	85 ± 10	86 ± 11	85 ± 10
Cholesterol (mg/dL)				
Total	236 ± 43	203 ± 41*	242 ± 39	246 ± 29†
HDL	64 ± 14	73 ± 20*	62 ± 12	63 ± 9†
LDL	143 ± 45	106 ± 45*	144 ± 50	145 ± 35†
Triglycerides (mg/dl)	145 ± 70	120 ± 49*	182 ± 67	199 ± 67†
CRP (mg/L)	3.94 ± 3.54	2.66 ± 2.49*	4.06 ± 2.67	3.85 ± 2.56†
Interleukin-6 (pg/ml)	6.25 ± 1.63	3.72 ± 0.95*	6.43 ± 2.13	5.83 ± 1.82†
Hemoglobin (g/dl)	14.5 ± 1.4	14.3 ± 1.2	14.7 ± 1.3	14.5 ± 1.2

Statines et HTAP des BPCO



Lee TM et al, Clin Sci (Lond). 2009

Usefulness of C-Reactive Protein and Interleukin-6 as Predictors of Outcomes in Patients With Chronic Obstructive Pulmonary Disease Receiving *Pravastatin*

Tsung-Ming Lee, MD[a], Mei-Shu Lin, PhD[b], and Nen-Chung Chang, MD, PhD[c,*]

(Am J Cardiol 2008;101:530–535)

Comparison of efficacy of pravastatin with placebo at baseline and after six months of therapy

Parameters	Pravastatin		Placebo	
	Baseline (n = 62)	Follow-up (n = 53)	Baseline (n = 63)	Follow-up (n = 54)
Exercise time on treadmill (s)	599 ± 323	922 ± 328*	608 ± 273	609 ± 180†
FEV_1 (%)	51 ± 18	55 ± 19	56 ± 13	55 ± 14
FEV_1 as percent forced expiratory vital capacity (%)	54 ± 11	58 ± 14	55 ± 8	54 ± 7
Total lung capacity (L)	5.00 ± 1.31	4.89 ± 1.11	5.09 ± 0.80	4.99 ± 1.35
Inspiratory capacity (L)	1.17 ± 0.52	1.33 ± 0.67	1.08 ± 0.83	1.19 ± 0.54
Borg dyspnea score	7.0 ± 0.8	4.0 ± 0.7*	6.9 ± 0.8	6.9 ± 1.0†

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

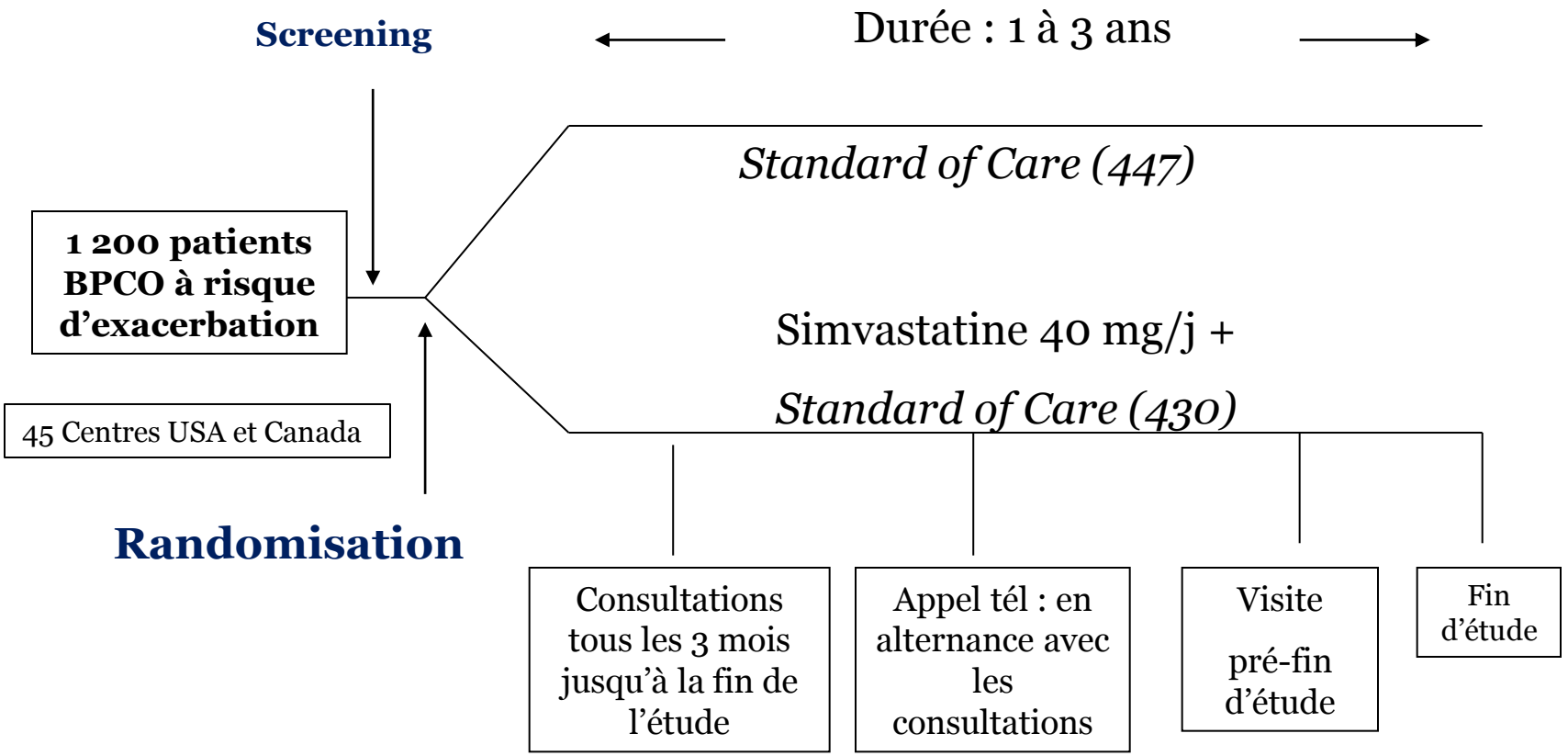
Simvastatin for the Prevention of Exacerbations in Moderate-to-Severe COPD

G.J. Criner, J.E. Connett, S.D. Aaron, R.K. Albert, W.C. Bailey, R. Casaburi, J.A.D. Cooper, Jr., J.L. Curtis, M.T. Dransfield, M.K. Han, B. Make, N. Marchetti, F.J. Martinez, D.E. Niewoehner, P.D. Scanlon, F.C. Sciurba, S.M. Scharf, D.D. Sin, H. Voelker, G.R. Washko, P.G. Woodruff, and S.C. Lazarus, for the COPD Clinical Research Network and the Canadian Institutes of Health Research

N ENGL J MED 370;23 NEJM.ORG JUNE 5, 2014

STATCOPE, NEJM 2014

STATCOPE: Méthodologie



STATCOPE, NEJM 2014

STATCOPE: Méthodologie

Critères d'inclusion:

- ***BPCO* 40 à 80 ans,**
- ***Tabagisme* ≥ 10 PA et/ou fumeurs actifs**
- ***Au moins un facteur de risque d'exacerbations:***

- Oxygénothérapie ,
- Corticothérapie systémique
- Antibiothérapie dans l'année précédente ;
- Consultation aux urgences ou hospitalisation pour exacerbation.

STATCOPE, NEJM 2014

STATCOPE: Méthodologie

Critères d'exclusion +++:

- Diabète
- Pathologies cardiovasculaires
- Patients sous statines
- Patients qui devraient être sous statines

STATCOPE, NEJM 2014

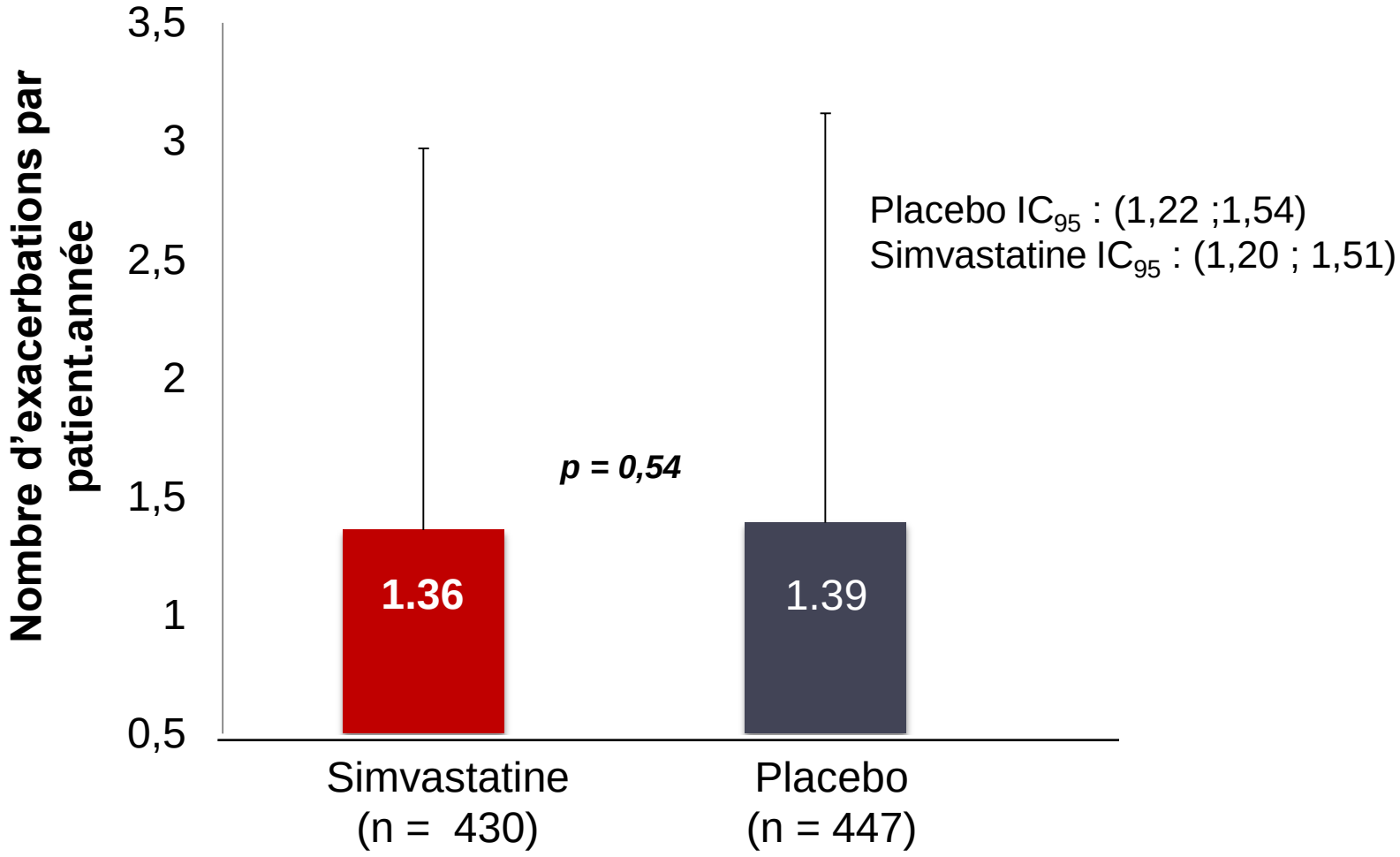
STATCOPE: Méthodologie

- **Critère principal :** Nombre moyen d'exacerbations par patient/année

- **Critères secondaires :**
  - Délai jusqu'à 1ère exacerbation
  - VEMS
  - Qualité de vie: Questionnaire Respiratoire de St George (SGRQ)
  - Sévérité des exacerbations

STATCOPE, NEJM 2014

STATCOPE: Résultats



STATCOPE, NEJM 2014

STATCOPE: Résultats

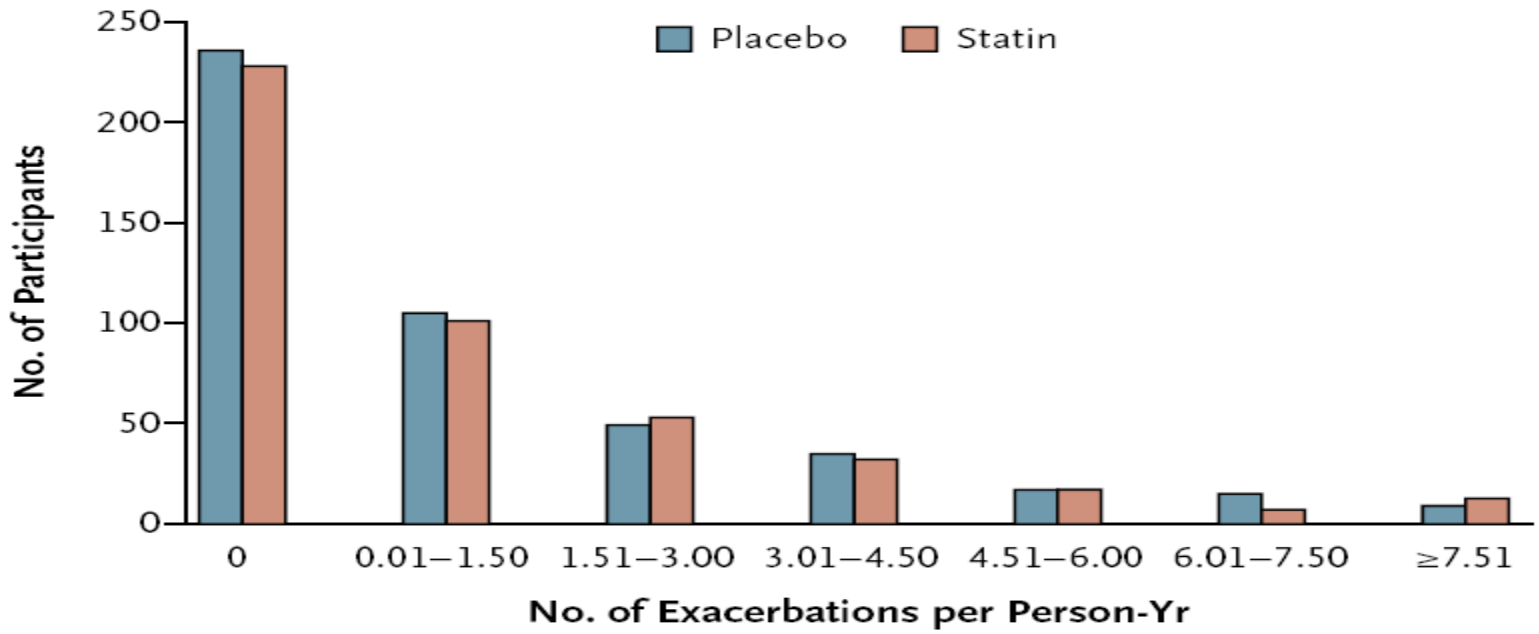


Figure 2. Acute Exacerbations of Chronic Obstructive Pulmonary Disease per Person-Year, According to Study Group.

The mean (±SD) number of exacerbations per person-year were similar in the simvastatin and placebo groups: 1.36±1.61 exacerbations per person-year and 1.39±1.73 exacerbations per person-year, respectively.

STATCOPE, NEJM 2014

STATCOPE: Résultats

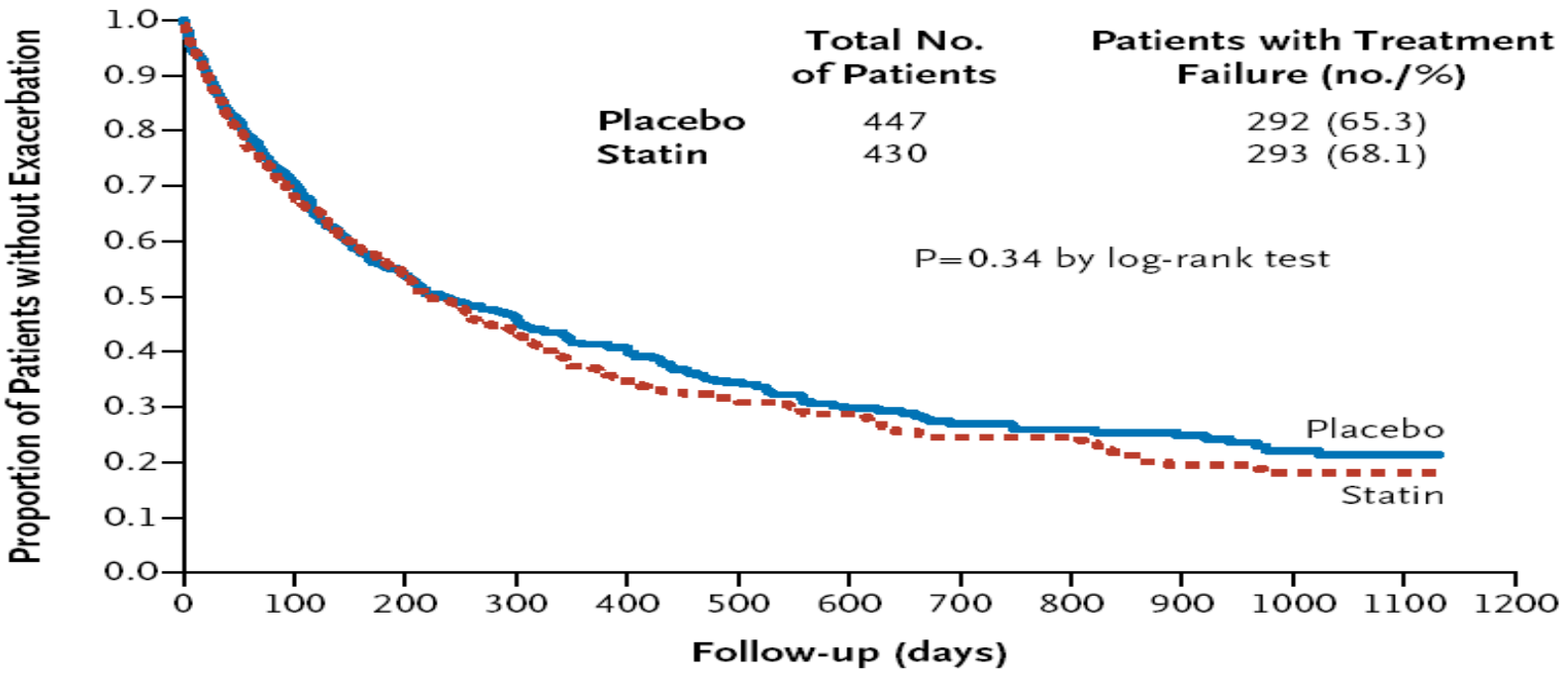


Figure 3. Effect of Simvastatin on the Time to the First Acute Exacerbation of Chronic Obstructive Pulmonary Disease.

There were no significant between-group differences in the time to the first exacerbation. The median time to the first exacerbation was 223 days (95% CI, 195 to 275) in the simvastatin group and 231 days (95% CI, 193 to 303) in the placebo group.

STATCOPE, NEJM 2014

STATCOPE: Tolérance des statines

Table 2. Nonfatal Serious Adverse Events and Fatal Events, According to Study Group.

Event	Simvastatin (N = 430)	Placebo (N = 447)	P Value
Nonfatal serious adverse event — no. of events/ person-yr			
Acute exacerbation	0.32	0.32	0.99
Respiratory event			
Pneumonia	0.01	<0.01	0.56
Chronic bronchitis	0.02	0.02	0.53
Other	0.01	0.01	0.75
Cardiovascular event			
Cardiac event	0.04	0.01	0.35
Other	0.03	0.08	0.23
Total	0.63	0.62	0.96
Fatal event — no. of patients (%)			
Acute exacerbation	6 (1.4)	5 (1.1)	0.72
Other respiratory event			
Pneumonia	1 (0.2)	1 (0.2)	0.99
Chronic bronchitis	0	2 (0.4)	0.16
Other	6 (1.4)	4 (0.9)	0.49
Total	28 (6.5)	30 (6.7)	0.89

STATCOPE, NEJM 2014

STATCOPE: Conclusions

- La simvastatine (40 mg/j) ne diminue pas le taux d'EABPCO modérées à sévères, ni le délai jusqu'à survenue d'une 1ère exacerbation.
- Aucun impact significatif sur la fonction respiratoire, la qualité de vie (SGRQ ; p = 0,38), les EI sévères ou la mortalité.

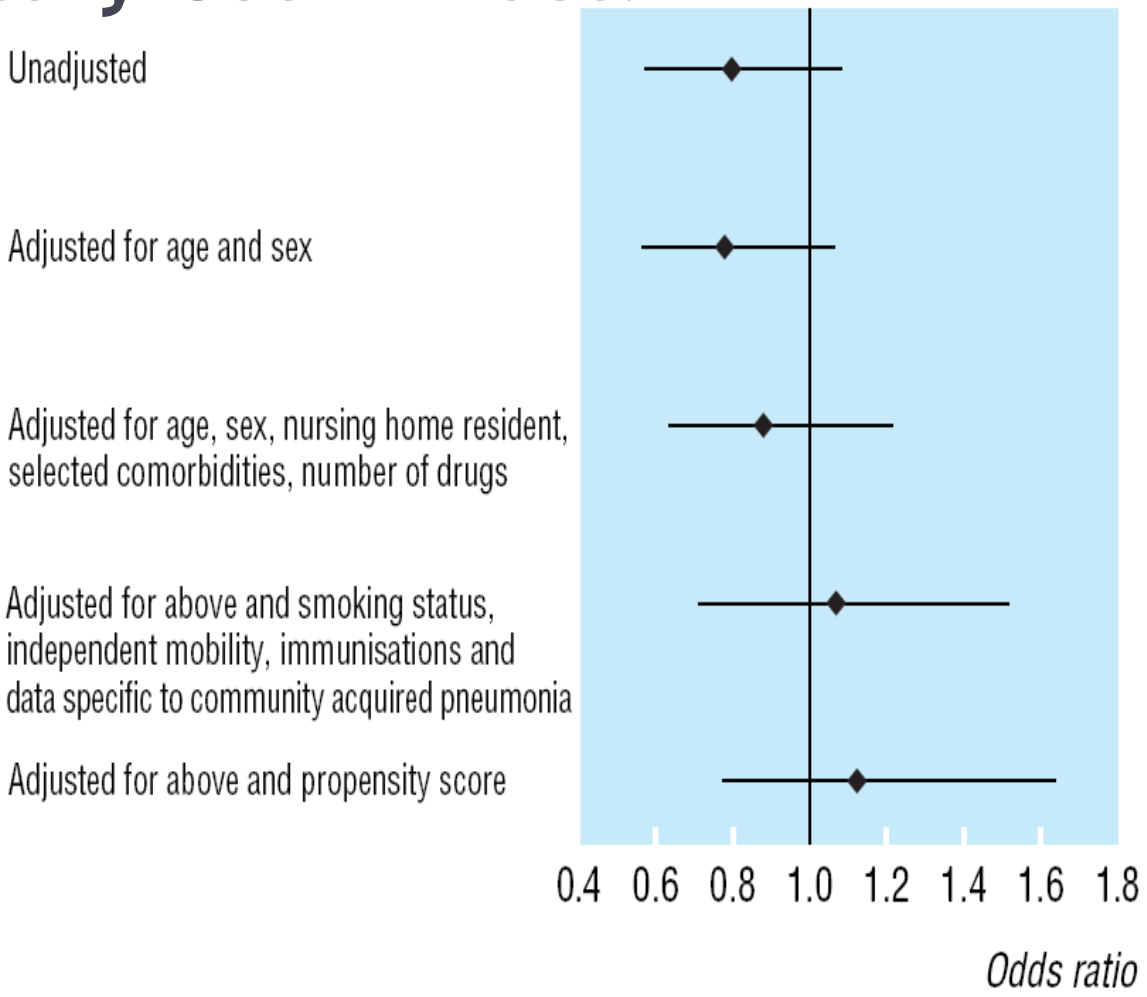
STATCOPE, NEJM 2014

Statines et BPCO

How Do We Cope After STATCOPE ?

Avenir des Statines chez les BPCO ?

Healthy User Effect?



Pneumonies (n=3415) Majumdar et al BMJ 2007

Immortal Time Bias?

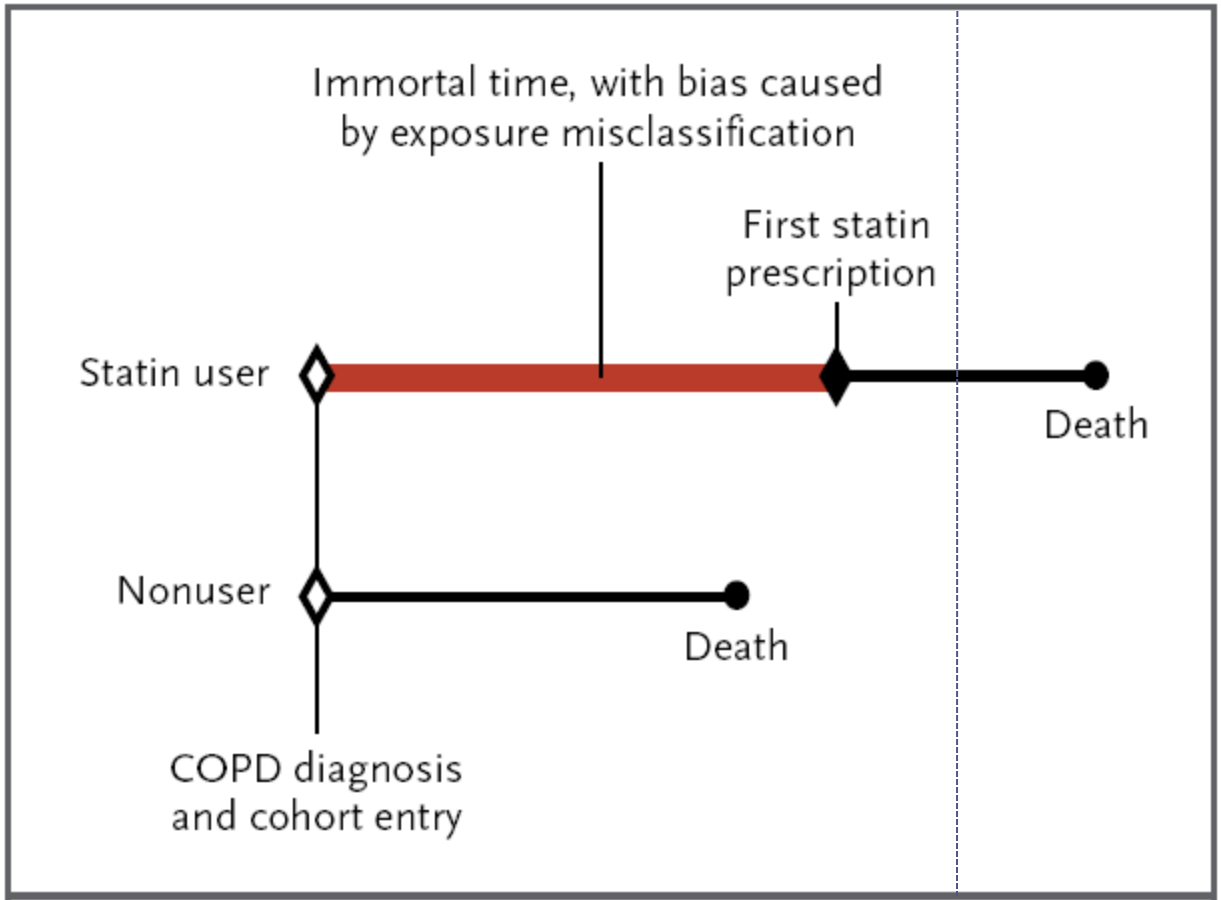


Figure 1. Immortal Time Bias.

Suissa S, NEJM 2014

Unhealthy Non-User effect?

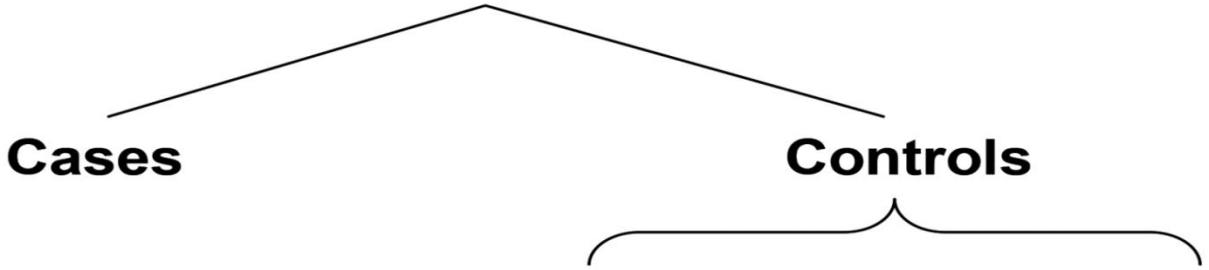
• Un grand nombre de BPCO **ayant des comorbidités cardiovasculaires** infracliniques ou non diagnostiquées, sont des **«non-utilisateurs»** des statines, mais qui pourraient en bénéficier.

• Ces patients: **mauvais pronostic** car:

Association de l'inflammation pulmonaire non traitée et de l'inflammation systémique non reconnue et des comorbidités cardiovasculaires infracliniques:

↳ **Risque accru d'EABPCO sévères** et une **mortalité plus élevée**.

Statines et BPCO:Observational Studies



Young RP, Thorax. 2014

Thorax Online First, published on October 27, 2014 as 10.1136/thoraxjnl-2014-205795

ORIGINAL ARTICLE

Statin use and exacerbations in individuals with chronic obstructive pulmonary disease

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- 5794 BPCO
- Copenhagen General Population (2003–2008).
- **Case-control design**,
- **Appariement sur**:

- L'âge,
- Le sexe,
- Le tabagisme,
- La sévérité de la BPCO (GOLD)
- **Les comorbidités.**

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- **Analyse brute**: réduction des EABPCO avec les statines **OR=0,68** (95% CI 0,51-0,91; p=0,01).
- **Analyse multivariée** par régression logistique: **OR=0,67** (0,48-0,92; p=0.01).
- Pas d'effet dans le **sous groupe** des BPCO sévères **sans comorbidités cardiovasculaires**: **OR=1,1** (0,5-2,1; p=0.83).

Conclusion

- Statines chez le BPCO sans aucune comormidité: **pas de preuve scientifique établie.**
- Chercher soigneusement les **comorbidités de la BPCO** (infracliniques) qui en constituent des **indications.**
- « **Statines or Not Statines** »: reste une question d'actualité dans la BPCO.
- **Etudes prospectives, randomisées** sont encore nécessaires.
- Pas d'études évaluant les statines **lors des EABPCO**?

Merci