

# Journal Club

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Z. Fumeaux

# Sharp Study

## The Study of Heart and Renal Protection

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The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial



# Background

Population générale: effet positif des statines sur les évènements cardiovasculaires en prévention primaire / secondaire ( ↓ 1/4 du risque pour chaque mmol/l de LDL abaissé)

Pas d'évidence chez les patients insuffisant rénaux

# Background

Si IRC modérée à sévère:

calcifications

rigidité vasculaire

médiacalcose

hyperactivité sympathique

# Background

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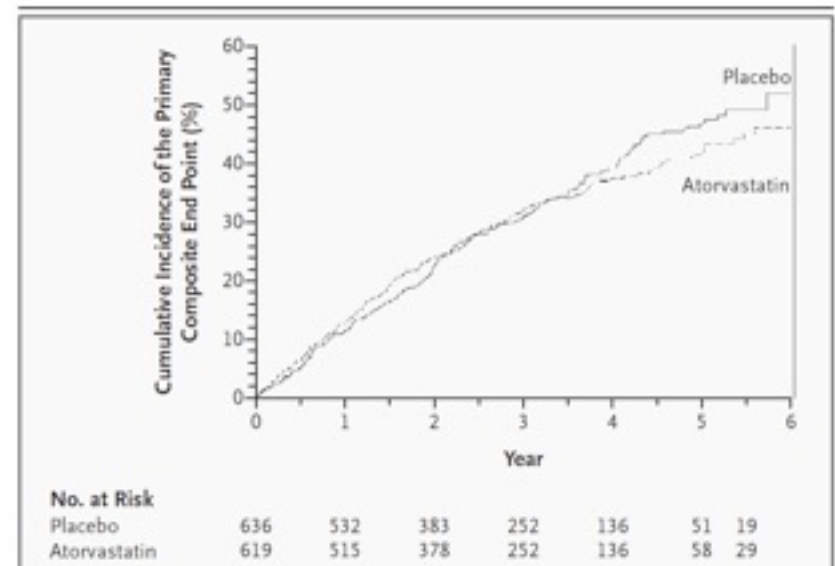
médiacalcose

hyperactivité sympathique

**Statines efficaces?**

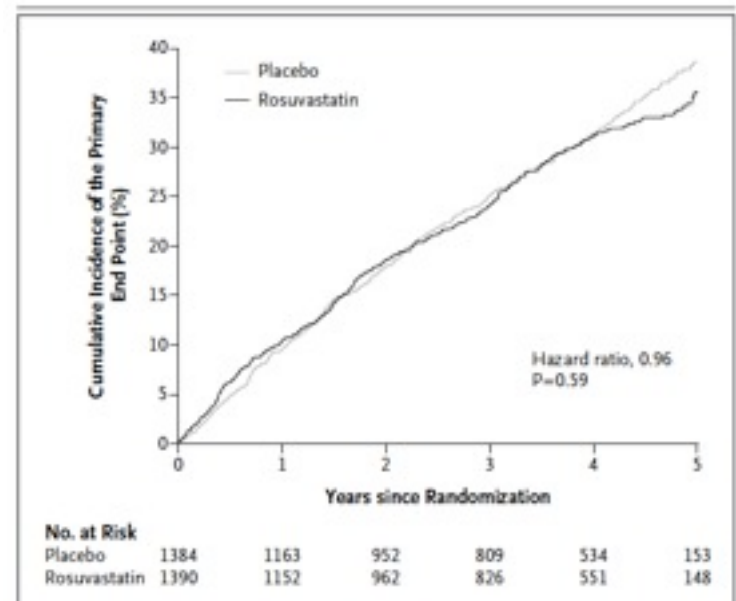
# Qu'avions nous jusqu'à maintenant?

- Etude 4 D: 2005  
Atorvastatine 20mg  
Diabétique HD  
Suivi 3.9 ans



# Qu'avions nous jusqu'à maintenant?

- Etude AURORA: 2009  
Rosuvastatine 10mg  
HD  
Suivi 3.9 ans



# Etude SHARP

Efficacité et sécurité de l'association:

Simvastatine 20mg

Ezetimibe 10mg

Sur la réduction du LDL cholest de 1mmol

Patients en IRC et IRT

# Etude SHARP

## Critères d'inclusion

- History of CKD
  - Predialysis (blood creatinine  $\geq 1.7$  mg/dL [ $\geq 150$   $\mu\text{mol/L}$ ] in men or  $\geq 1.5$  mg/dL [ $\geq 130$   $\mu\text{mol/L}$ ] in women at both the most recent routine clinic visit and the study screening visit) or
  - Dialysis (hemodialysis or peritoneal dialysis)
- Men or women aged  $\geq 40$  years

# Etude SHARP

## Critères d'exclusion

- Definite history of MI or coronary revascularization procedure
- Functioning renal transplant or living donor renal transplant planned
- Less than 2 months since presentation as an acute uremic emergency
- Definite history of chronic liver disease or abnormal liver function (ie, ALT >1.5× ULN or, if ALT not available, AST >1.5× ULN) (patients with a history of hepatitis are eligible if these limits are not exceeded)
- Evidence of active inflammatory muscle disease (eg, dermatomyositis, polymyositis) or CK >3× ULN
- Definite previous adverse reaction to a statin or to ezetimibe
- Concurrent treatment with a contraindicated drug:
  - Hydroxymethylglutaryl-coenzyme A reductase inhibitor ("statin")
  - Ezetimibe
  - Fibric acid derivative ("fibrate")
  - Nicotinic acid
  - Cyclosporin
  - Macrolide antibiotic (erythromycin, clarithromycin)
  - Systemic use of imidazole or triazole antifungals (eg, itraconazole, ketoconazole)
  - Protease-inhibitors (eg, antiretroviral drugs for HIV infection)
  - Nefazodone
- Child-bearing potential (ie, premenopausal woman who is not using a reliable method of contraception)
- Known to be poorly compliant with clinic visits or prescribed medication
- Medical history that might limit the individual's ability to take the trial treatments for the duration of the study (eg, severe respiratory disease, history of cancer other than nonmelanoma skin cancer, or recent history of alcohol or substance misuse)

# Etude SHARP

- **Statistiques**

Réduction d'un  $\frac{1}{4}$  des évènements CV pour 1mmol/l de diminution du LDL

Dans IRC 1/5 des évènements ne sont pas athérosclérotiques → diminution de 20% du risque

Incidence annuelle des évènements chez les patients de SHARP (IRC et IRT): 3.7% → 4 ans de suivi

Puissance 90% et marge d'erreur 0.01 → 1100 évènements

Incidence IRT est de 20% sur un suivi de 4 ans → 6000 patients pour détecter diminution de 20% du RR d'IRT

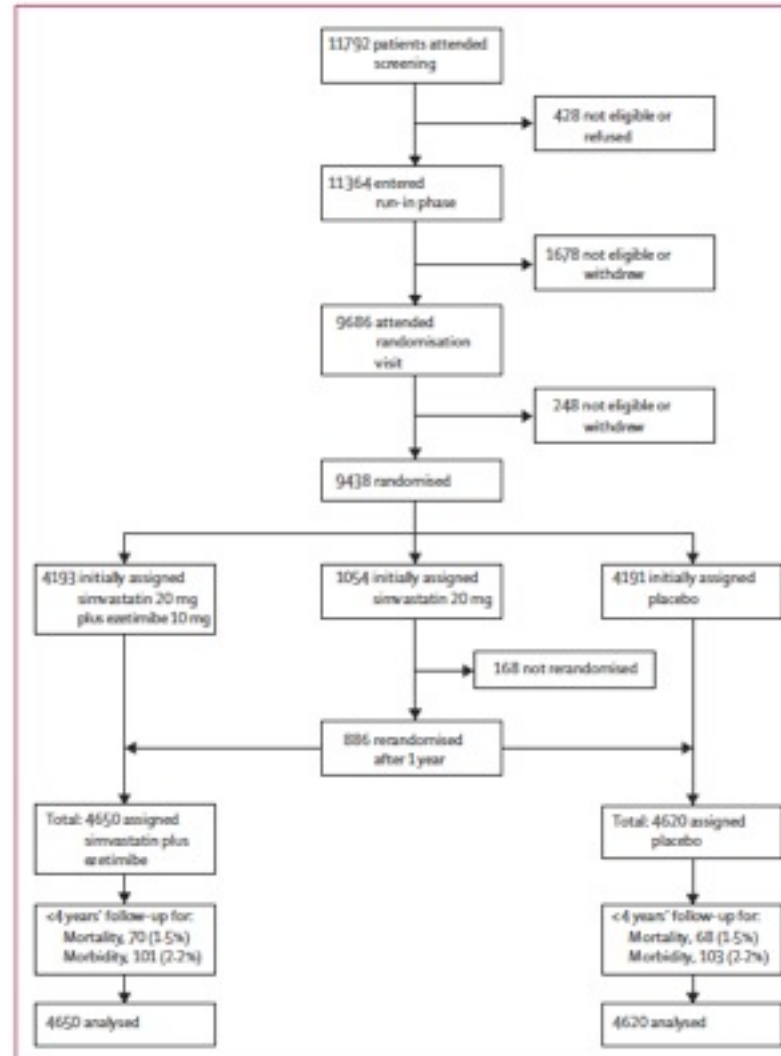
# Etude SHARP

- 18 pays, 380 hôpitaux
- Juin 2003 et juin 2006

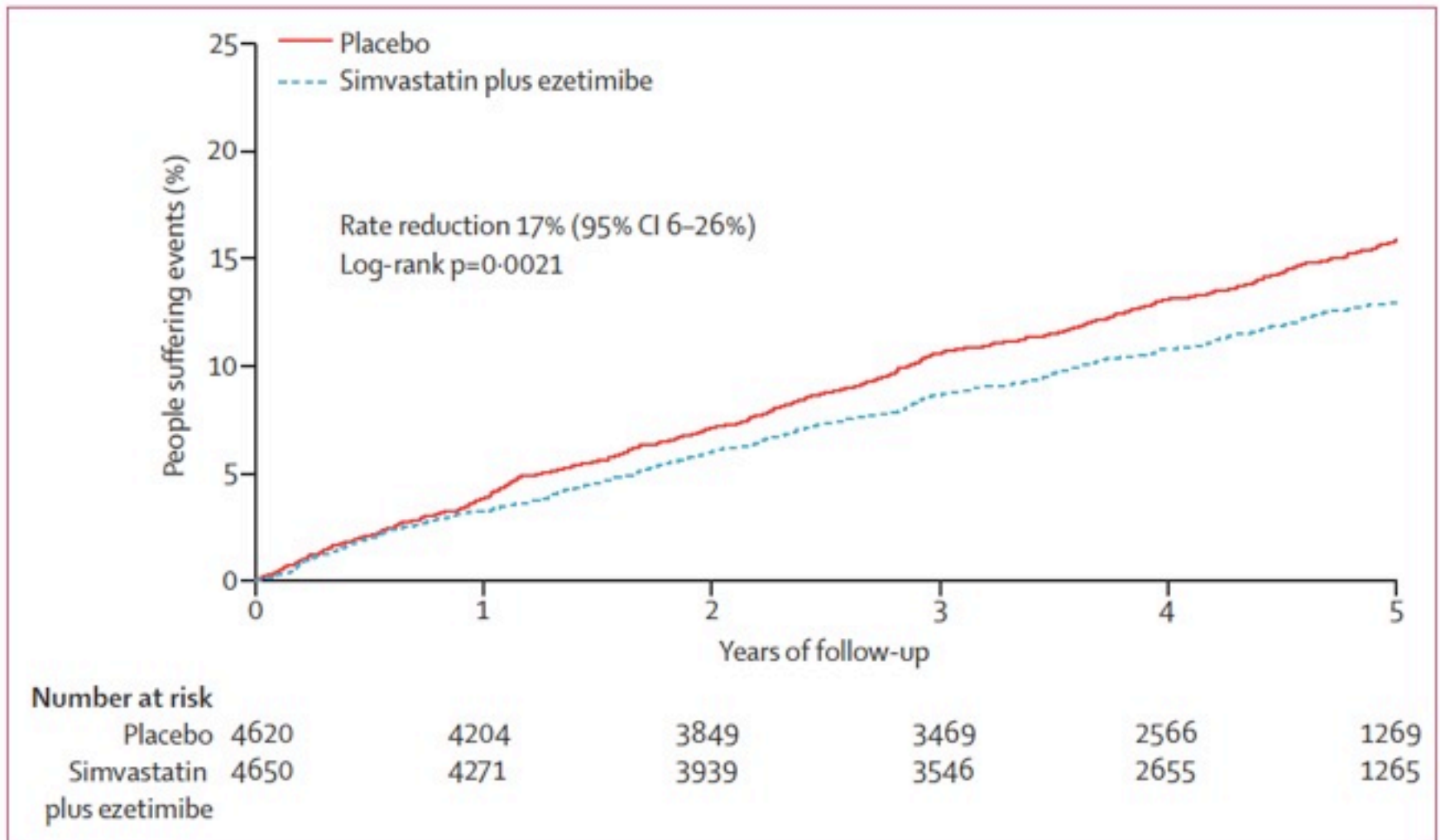
# Etude SHARP: démographie

	Not on dialysis	On dialysis	All patients
Number randomized	6382	3056	9438
Renal diagnosis			
Glomerulonephritis	1063 (17%)	689 (23%)	1752 (19%)
Diabetic nephropathy	916 (15%)	477 (16%)	1393 (15%)
Hypertensive or renovascular disease	1334 (22%)	482 (16%)	1816 (20%)
Cystic kidney disease	690 (11%)	374 (12%)	1064 (12%)
Pyelonephritis/obstructive nephropathy	413 (7%)	202 (7%)	615 (7%)
Other known cause	911 (15%)	373 (12%)	1284 (14%)
Unknown cause	796 (13%)	403 (13%)	1199 (13%)
Unavailable	259	56	315
Age, y			
Mean (SD)	62.3 (11.7)	58.9 (11.8)	61.2 (11.9)
40-49	1099 (17%)	825 (27%)	1924 (20%)
50-59	1516 (24%)	826 (27%)	2342 (25%)
60-69	1794 (28%)	740 (24%)	2534 (27%)
70+	1973 (31%)	665 (22%)	2638 (28%)
Sex			
Men	3954 (62%)	1946 (64%)	5900 (63%)
Women	2428 (38%)	1110 (36%)	3538 (37%)
Physical measurements			
Systolic blood pressure, mm Hg	139 (21)	139 (24)	139 (22)
Diastolic blood pressure, mm Hg	80 (13)	78 (13)	79 (13)
Body mass index, kg/m <sup>2</sup>	27.4 (5.5)	26.4 (5.8)	27.1 (5.6)
Waist circumference, cm	96.7 (14.8)	97.0 (15.7)	96.8 (15.1)
Smoking			
Current smoker	791 (12%)	475 (16%)	1266 (13%)
Prior diseases*			
Angina	212 (3%)	77 (3%)	289 (3%)
Peripheral arterial disease	371 (6%)	229 (7%)	600 (6%)
Cerebrovascular disease	464 (7%)	187 (6%)	651 (7%)
Any vascular disease	933 (15%)	437 (14%)	1370 (15%)
Diabetes	1429 (22%)	650 (21%)	2079 (22%)
Ethnic group			
White	4567 (72%)	2206 (72%)	6773 (72%)
Black	130 (2%)	146 (5%)	276 (3%)
Chinese	1031 (16%)	109 (4%)	1140 (12%)
Other Asian	528 (8%)	442 (14%)	970 (10%)
Other/not specified	126 (2%)	153 (5%)	279 (3%)

# Etude SHARP: Profile



# Etude SHARP: Résultats



# Etude SHARP: sécurité de l'ézétimibe

	Placebo	Simvastatin only	Ezetimibe plus simvastatin	P <sup>a</sup>	P <sup>b</sup>
Number randomized	4191	1054	4193		
Muscle pain	393 (9.4%)	103 (9.8%)	430 (10.3%)	.19	.68
CK					
>5x but ≤10 x ULN					
Asymptomatic	11 (0.3%)	5 (0.5%)	16 (0.4%)	.44	.88
Muscle symptoms present	3 (0.1%)	1 (0.1%)	1 (0.0%)	.62	.86
>10x but ≤40 x ULN					
Not on dialysis <sup>c</sup>					
No end-organ damage <sup>d</sup>					
Asymptomatic	0 (0.0%)	1 (0.1%)	0 (0.0%)	–	.46
Muscle symptoms present	0 (0.0%)	0 (0.0%)	0 (0.0%)	–	–
With end-organ damage <sup>d</sup>	4 (0.1%)	0 (0.0%)	1 (0.0%)	.37	1.0
On dialysis <sup>c</sup>					
Asymptomatic	1 (0.0%)	0 (0.0%)	2 (0.0%)	1.0	1.0
Muscle symptoms present	0 (0.0%)	0 (0.0%)	1 (0.0%)	1.0	1.0
>40x ULN					
Not on dialysis <sup>c</sup>					
With end-organ damage <sup>d</sup>	1 (0.0%)	0 (0.0%)	0 (0.0%)	1.0	–
Persistently elevated liver transaminases <sup>e</sup>	5 (0.1%)	0 (0.0%)	7 (0.2%)	.77	.39
Hepatitis <sup>f</sup>					
Infective	6 (0.1%)	1 (0.1%)	6 (0.1%)	1.0	1.0
Noninfective	1 (0.0%)	0 (0.0%)	2 (0.0%)	1.0	1.0
No cause identified	1 (0.0%)	1 (0.1%)	2 (0.0%)	1.0	1.0
Complications of gallstones					
Acute pancreatitis	5 (0.1%)	0 (0.0%)	4 (0.1%)	1.0	.70
Other complications	19 (0.5%)	3 (0.3%)	17 (0.4%)	.87	.77
Hospitalization with gallstones <sup>g</sup>	4 (0.1%)	4 (0.4%)	2 (0.0%)	.68	.02
Pancreatitis					
Acute (excluding gallstones)	7 (0.2%)	1 (0.1%)	2 (0.0%)	.18	1.0
Chronic	1 (0.0%)	0 (0.0%)	0 (0.0%)	1.0	–

# SHARP: Guides primaires

## Allocation des patients au traitement randomisé

### **Randomisation and masking**

At the end of the run-in period, patients who agreed to continue were allocated the study treatment by the local study laptop computer with minimised randomisation<sup>14</sup> (which balanced for age, sex, ethnic origin, dialysis *vs* non-dialysis, prior vascular disease, previous diabetes, systolic blood pressure, creatinine, and total cholesterol).

Allocation cachée? Etablissement d'une liste de randomisation?  
Stratification par centre?

# SHARP: Guides primaires

Follow up complet?

Durée adéquate (4,9 ans)

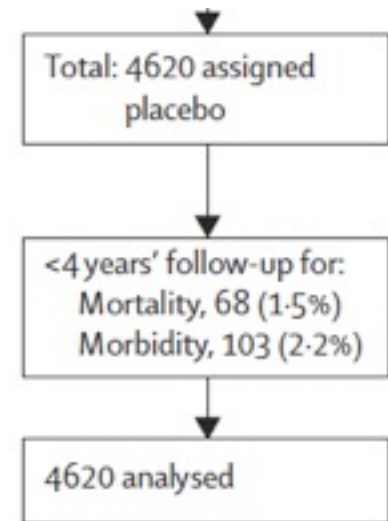
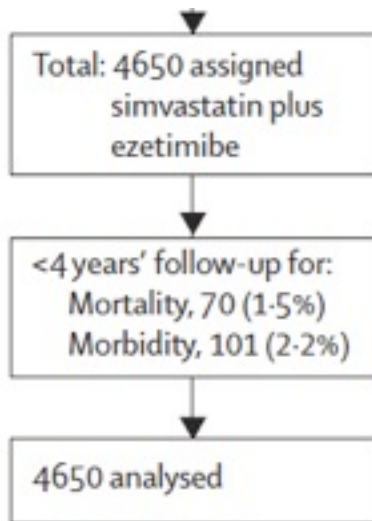
Très peu de patients perdus

# SHARP: Guides primaires

Analyse des patients dans les groupes:

Pas de cross over.

Etude ITT



	LDL-cholesterol-lowering drug use		
	Simvastatin plus ezetimibe	Placebo	Absolute difference
8-13 months	77%	3%	74%
26-31 months	71%	9%	61%
44-49 months	68%	14%	55%

# SHARP: Guides secondaires

## Blinding:

Double blinding

Evaluation aveugle des issues?

This information was sent to the international coordinating centre for central adjudication, in accordance with prespecified definitions, by trained clinicians who were masked to study treatment allocation.

# SHARP: Guides secondaires

Groupes semblables au début du traitement?

Le nombre de patient et la stratification de la randomisation: pas de différence -> cf table 1

	Simvastatin plus ezetimibe (n=4650)	Placebo (n=4620)
Previous vascular disease*	711 (15%)	682 (15%)
Diabetes*	1054 (23%)	1040 (23%)
Men	2915 (63%)	2885 (62%)
Age at randomisation (years)*	62 (12)	62 (12)
Current smoker	626 (13%)	608 (13%)
Diastolic blood pressure (mm Hg)*	79 (13)	79 (13)
Systolic blood pressure (mm Hg)*	139 (22)	139 (22)
Total cholesterol (mmol/L)	4.88 (1.20)	4.90 (1.17)
LDL cholesterol (mmol/L)	2.77 (0.88)	2.78 (0.87)
HDL cholesterol (mmol/L)	1.12 (0.35)	1.11 (0.34)
Triglycerides (mmol/L)	2.31 (1.76)	2.34 (1.68)
Body-mass index (kg/m <sup>2</sup> )*	27.1 (5.7)	27.1 (5.6)
Renal status		
On dialysis	1533 (33%)	1490 (32%)
Haemodialysis	1275 (27%)	1252 (27%)
Peritoneal dialysis	258 (6%)	238 (5%)
Not on dialysis†	3117 (67%)	3130 (68%)
MDRD-estimated GFR (mL/min per 1.73 m <sup>2</sup> )*‡§		
Mean (SD)	26.6 (12.9)	26.6 (13.1)
≥60	44 (1%)	44 (1%)
≥30 to <60	1100 (37%)	1055 (35%)
≥15 to <30	1246 (41%)	1319 (44%)
<15	614 (20%)	607 (20%)
Not available	113	105
Urinary albumin:creatinine ratio (mg/g)‡§		
Median (IQR)	217 (44-788)	196 (43-748)
<30	545 (20%)	562 (20%)
≥30 to ≤300	1032 (37%)	1076 (39%)
>300	1203 (43%)	1156 (41%)
Not available	337	336

# SHARP: Guides secondaires

Groupes traités de façon égale?

Pas d'informations

Prise en charge laissée au gré de l'investigateur local.

Pas de stratification par centre

# SHARP: Résultats

## Choix de l'outcome primaire

Temps jusqu'au premier événement d'un EP composite (changé au cours de l'étude)

The annual incidence of major vascular events in SHARP (defined as non-fatal myocardial infarction or any cardiac death, any stroke, or any arterial revascularisation excluding dialysis access procedures)

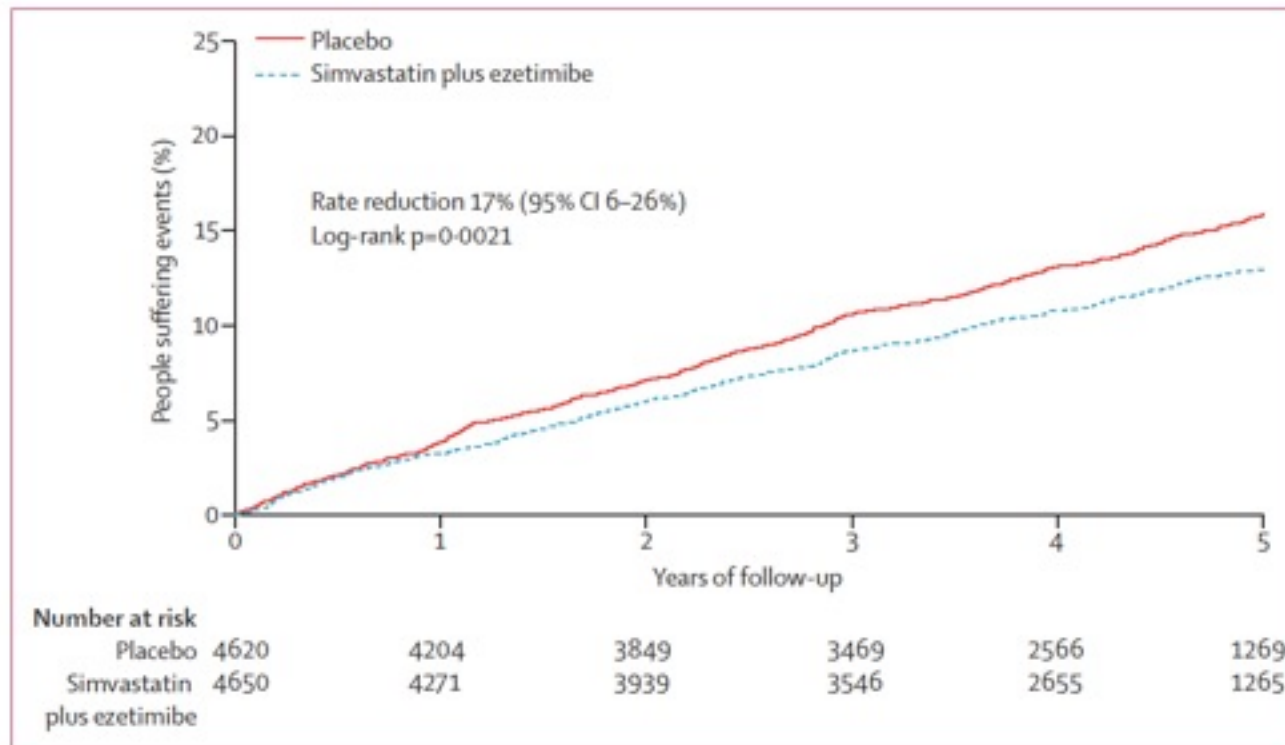
decided that the key study outcome should be changed to major atherosclerotic events (defined as non-fatal myocardial infarction or coronary death, non-haemorrhagic stroke, or arterial revascularisation excluding dialysis access procedures) and the key comparison should be between all patients ever allocated simvastatin plus ezetimibe versus placebo (including those initially allocated

Problème des outcome composites: poids des composants et fréquences relatives différentes

Objectivité garantie par l'analyse centrale

# SHARP: Résultats

## Grandeur de l'effet du traitement



# SHARP: Résultats

Précision de l'estimation de l'effet du traitement

Résultats conformes à l'hypothèse initiale

# SHARP: Applicabilité

Résultats applicables à mes patients?

Oui

Toutes les issues ont été considérées?

Changement de l'EP primaire

Pourquoi ézétimibe? Groupe simvastatine seule

Bénéfices versus effets secondaires et couts?

oui