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RESEARCH

Effect of statins on atrial fibrillation: collaborative meta-analysis of published and unpublished evidence from randomised controlled trials

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Background et objectif

- La Fibrillation Auriculaire (FA) constitue le trouble de rythme le plus fréquent, dont la prévalence augmente avec l'âge.
- FA: cause de multiples morbidité et mortalité
- 2 méta-analyses récentes ont montré que les statines, à court terme, diminuent le risque de survenue de FA
- **Objectif**: déterminer si les statines, à long terme, réduisent le risque de survenue de FA

Matériels & Méthodes

- Méta-analyse
- Incluant toutes les études randomisées contrôlées, publiées ou non, ayant pour sujet FA/statine
- Sources de données: Medline, Embase, Cochrane
- Pour les études non publiées, les informations sont recueillies au près des investigateurs

Résultats

- Sont inclus:
 - 13 études dites de court terme, comparant deux groupes (groupe statines versus groupe contrôle).
 - 29 études à long court non publiées, dont 22 comparent statine vs contrôle et 7 comparent statine forte dose vs statine faible dose

Table 1| Summary of characteristics of short term trials on effect of statins

Study	Mean follow-up (years)	Country / region	Intervention/ control	Main inclusion criteria	Brent capturing methods	No in intervention / control	Mean age (years)	Male (%)	Previous MI (%)	Potential risk of bias
Tveit et al, 2004 ¹⁹	0.12	Norway	Pravastatin 40 mg/ no treatment	Cardioversion	Serial ECG recording	51/51	68	87	—	Unclear
MIRACL, 2004 ²⁰	0.31	Multinational	Atorvastatin 80 mg/ placebo	Acute coronary syndrome	Serial ECG recording	1538/1548	65	65	25	Low
Dernellis et al, 2005 ²¹	0.42	Greece	Atorvastatin 20-40 mg/ placebo	Paroxysmal atrial fibrillation	48 hour ambulatory ECG once during follow-up	40/40	52*	65	—	Unclear
ARMYDA-3, 2006 ²²	0.08	Italy	Atorvastatin 40 mg/ placebo	Planned cardiac surgery	Continuous ECG monitoring for 6 days followed by daily ECG recording until discharge	101/99	66	74	43	Low
Chello et al, 2006 ²³	0.06	Italy	Atorvastatin 20 mg/ placebo	Planned CABG	Postoperative monitoring	20/20	65	78	—	Unclear
Ozaydin et al, 2006 ²⁴	0.25	Turkey	Atorvastatin 10 mg/ no treatment	Cardioversion	24 hour ambulatory ECG monitoring at 1 and 3 month follow-up	24/24	62	60	0	High
Garcia-Fernandez et al, 2006 ²⁵	0.08	Spain	Atorvastatin 80 mg/ no treatment	Cardioversion	ECG recording at 3 months or clinical event	27/25	—	—	—	High
Song et al, 2008 ²⁶	0.02	Korea	Atorvastatin 20 mg/ no treatment	Planned CABG	Continuous ECG monitoring until discharge	62/62	63	40	7	High
Mannacio et al, 2008 ²⁷	0.05	Italy	Rosuvastatin 20 mg/ placebo	Planned CABG	Postoperative monitoring	100/100	73	60	23	Low
Tamayo et al, 2008 ²⁸	0.39	Spain	Simvastatin 20 mg/ no treatment	Planned CABG	Postoperative monitoring	22/22	68	65	0	High
Almroth et al, 2009 ²⁹	0.13	Sweden	Atorvastatin 80 mg/ placebo	Cardioversion	Serial ECG recording	118/116	65	76	—	Low
Xia et al, 2009 ³⁰	0.25	China	Rosuvastatin 20 mg/ no treatment	Cardioversion	24 hour ambulatory ECG monitoring	32/32	61	98	—	Unclear
Jiet et al, 2009 ³¹	0.04	China	Atorvastatin 20 mg/ placebo	Planned CABG	Continuous ECG monitoring 7 days followed by daily ECG recording until discharge	71/69	66	49	—	Low

MI=myocardial infarction; ECG=electrocardiography; CABG=coronary artery bypass graft surgery.

*Median.

Table 2 | Summary of characteristics of longer term (with at least six months' follow-up) hypercholesterolaemia treatment trials: statin versus control regimen

Study	Mean follow-up (years)	Country/region	Intervention/control	Main inclusion criteria	Event capturing methods	No in intervention/control	Mean age (years)	Male (%)	Previous MI (%)	Potential risk of bias
WOSCOPS, 1995 ²⁴	4.8	UK	Pravastatin 40 mg/placebo	Primary prevention	Periodic ECG recording	3302/3293	55	100	0	Low
ARCARE/TextCAPS, 1996 ²⁵	5.3	USA	Lovastatin 20-40 mg/placebo	Primary prevention	Unpublished AE reports	3304/3301	58	85	0	Low
GISSI-P, 2000 ²⁶	1.9	Italy	Pravastatin 20 mg/no treatment	Recent MI	Unpublished AE reports	2138/2133	60	86	100	Low
ALLIANCE I, 2002 ²⁷	4.8	North America	Pravastatin 40 mg/usual care	Hypertension plus other risk factor	Periodic ECG recording	4327/4255	66	51	0	Low
HPS, 2002 ²⁸	5.0	UK	Simvastatin 40 mg/placebo	Vascular disease or diabetes	Unpublished AE reports	10 269/10 267	64	75	4.1	Low
LIPS, 2002 ²⁹	3.1	Europe, Canada, Brazil	Fluvastatin 80 mg/placebo	Post-PCI	Unpublished AE reports	844/833	60	84	4.4	Low
ROSCOR, 2002 ³⁰	3.2	Scotland, Ireland, Netherlands	Pravastatin 40 mg/placebo	Eligible with vascular disease or high risk	Periodic ECG recording, unpublished	2891/2913	70	48	1.0	Low
ASCOT-LLA, 2003 ³¹	3.2	Nordic, UK, Ireland	Atorvastatin 10 mg/placebo	Hypertension plus other risk factor	Unpublished AE reports	5168/5137	65	81	0	Low
ALLANCE II, 2004 ³²	4.3	USA	Atorvastatin 10-40 mg/usual care	CHD	Unpublished AE reports	1217/1225	61	82	5.8	Low
CARDIC, 2004 ³³	3.9	UK, Ireland	Atorvastatin 10 mg/placebo	Type 2 diabetes plus other risk factor	Unpublished AE reports	1428/1410	62	68	0	Low
REVENOIT, 2004 ³⁴	3.8	Netherlands	Pravastatin 40 mg/placebo	Microalbuminuric patients	Unpublished AE reports	433/431	51	65	0	Low
PCAD, 2005 ³⁵	4.5	Japan	Pravastatin 10-20 mg/usual care	After CADG	Unpublished AE reports	168/167	59	85	62	Low
GD, 2005 ³⁶	3.9	Germany	Atorvastatin 20 mg/placebo	Haemodialysis patients with diabetes	Unpublished AE reports	619/626	66	54	1.8	Low
MEGA, 2006 ³⁷	5.3	Japan	Pravastatin 10-20 mg/no treatment	Primary prevention	Unpublished AE reports	3866/3966	58	32	0	Low
ASPIN, 2006 ³⁸	4.3	Multinational	Atorvastatin 10 mg/placebo	Type 2 diabetes	Unpublished AE reports	1211/1199	61	66	1.6	Low
Sola, 2006 ³⁹	1.0	USA	Atorvastatin 20 mg/placebo	Non-ischaemic CHF	Unpublished AE reports	54/54	54	34	0	Low
GISSI-HF, 2006 ⁴⁰	3.9	Italy	Rosuvastatin 10 mg/placebo	CHF	Serial ECG recording and AE reports	1855/1835	68	77	3.2	Low
ATMEDI, 2006 ⁴¹	1.0	Taiwan	Atorvastatin 20 mg/usual care	Pacemaker for bradyarrhythmias	Pacemaker interrogation	52/54	71	45	0	High
Vitovec et al, 2006 ⁴²	1.0	Slovenia	Atorvastatin 10 mg/usual care	CHF	Unpublished AE reports	55/55	63	61	5.9	Low
MITOIR, 2006 ⁴³	2.0	Multinational	Rosuvastatin 40 mg/placebo	Low risk for cardiovascular event	Unpublished AE reports	702/702	57	60	0	Low
JUPITER, 2007 ⁴⁴	1.8	Multinational	Rosuvastatin 20 mg/placebo	Primary prevention	Unpublished AE reports	8901/8901	66	62	0	Low
LEADER, 2010 ⁴⁵	1.5	Multinational	Atorvastatin 80 mg/placebo	Mild to moderate probable Alzheimer's disease	Unpublished AE reports	314/326	74	48	0	Low

ECG = electrocardiography; AE = adverse event; MI = myocardial infarction; CHD = coronary heart disease; CADG = coronary artery bypass graft surgery; CHF = chronic heart failure; PCI = percutaneous coronary intervention.

Table 3 | Summary of characteristics of longer term (with at least six months' follow-up) hypothesis testing trials: more intensive versus less intensive statin treatment

Study	Mean follow-up (years)	Country/region	Intervention/control	Main inclusion criteria	Event capturing methods	No in Intervention/control	Mean age (years)	Male (%)	Previous MI (%)	Potential risk of bias
A-2, 2004 ²⁴	2.0	Multinational	Simvastatin 80 mg/20 mg	Acute coronary syndrome	Published All reports	2265/2238	61	76	17	Low
REVERSAL, 2004 ²⁵	1.5	USA	Atorvastatin 80 mg/pasivated n40 mg	>30% stenosis on initial coronary angiogram	Unpublished All reports	228/229	56	73	0	Low
PRODIGY, 2004 ²⁴	2.0	Multinational	Atorvastatin 80 mg/pasivated n40 mg	Acute coronary syndrome	Published All reports	2099/2049	58	78	18	Low
TNT, 2005 ²⁵	4.9	Multinational	Atorvastatin 80 mg/10 mg	Clinically evident CHD	Unpublished All reports	4995/5006	61	81	58	Low
LOGAL, 2005 ²⁴	4.8	Sweden, Netherlands, Iceland	Atorvastatin 40-80 mg/ simvastatin 20-40 mg	Myocardial infarction	Unpublished All reports	4439/4449	62	81	100	Low
Schirmer et al, 2006 ²⁷	1	Germany	Atorvastatin 80 mg/10 mg	No obstructive CHD	Published All report	276/274	61	75	0	low
Colicchi et al, 2010 ²⁸	0.7	Italy	Atorvastatin 80 mg/20-40 mg	Acute presentation of severe CHD	Unpublished All reports	144/146	75	48.6	100	Low

MI=myocardial infarction; All=all events; CHD=coronary heart disease.

Résultats

- Les études de court terme ont montré que le traitement par les statines diminuent le risque de survenue de FA OR =0.39
- À long terme: - les statines ne modifient pas le risque de survenue de la FA en comparaison avec le groupe contrôle (2.3% groupe statine vs 2.5% groupe contrôle)
 - le risque de survenue de FA est de 4.9% pour les deux groupes statine forte dose et statine faible dose

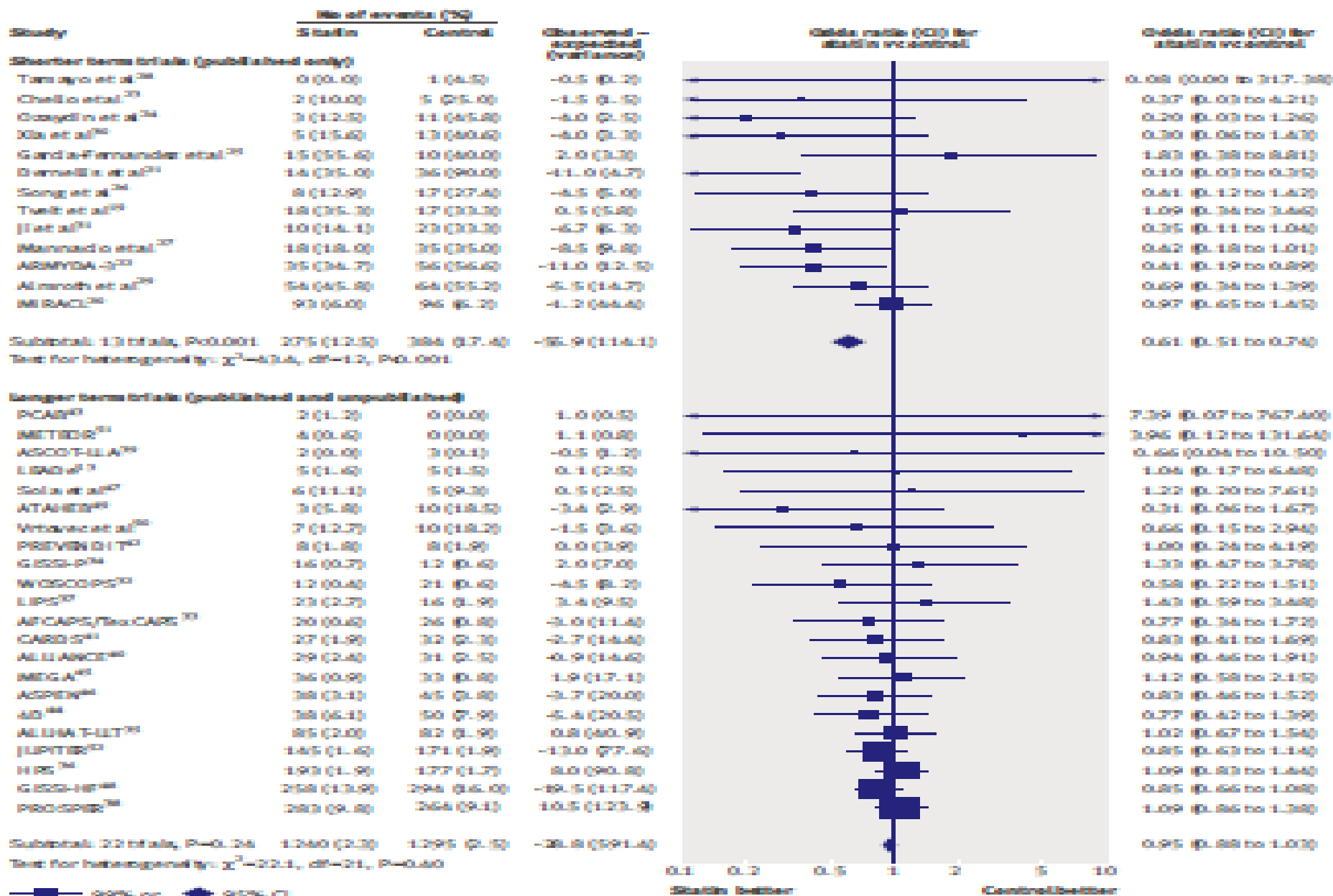


Fig 2 Effect of statin treatment on atrial fibrillation in 13 shorter and 22 longer term trials of statin vs control (test for difference: $\chi^2=18.6$, df=1, P<0.001)

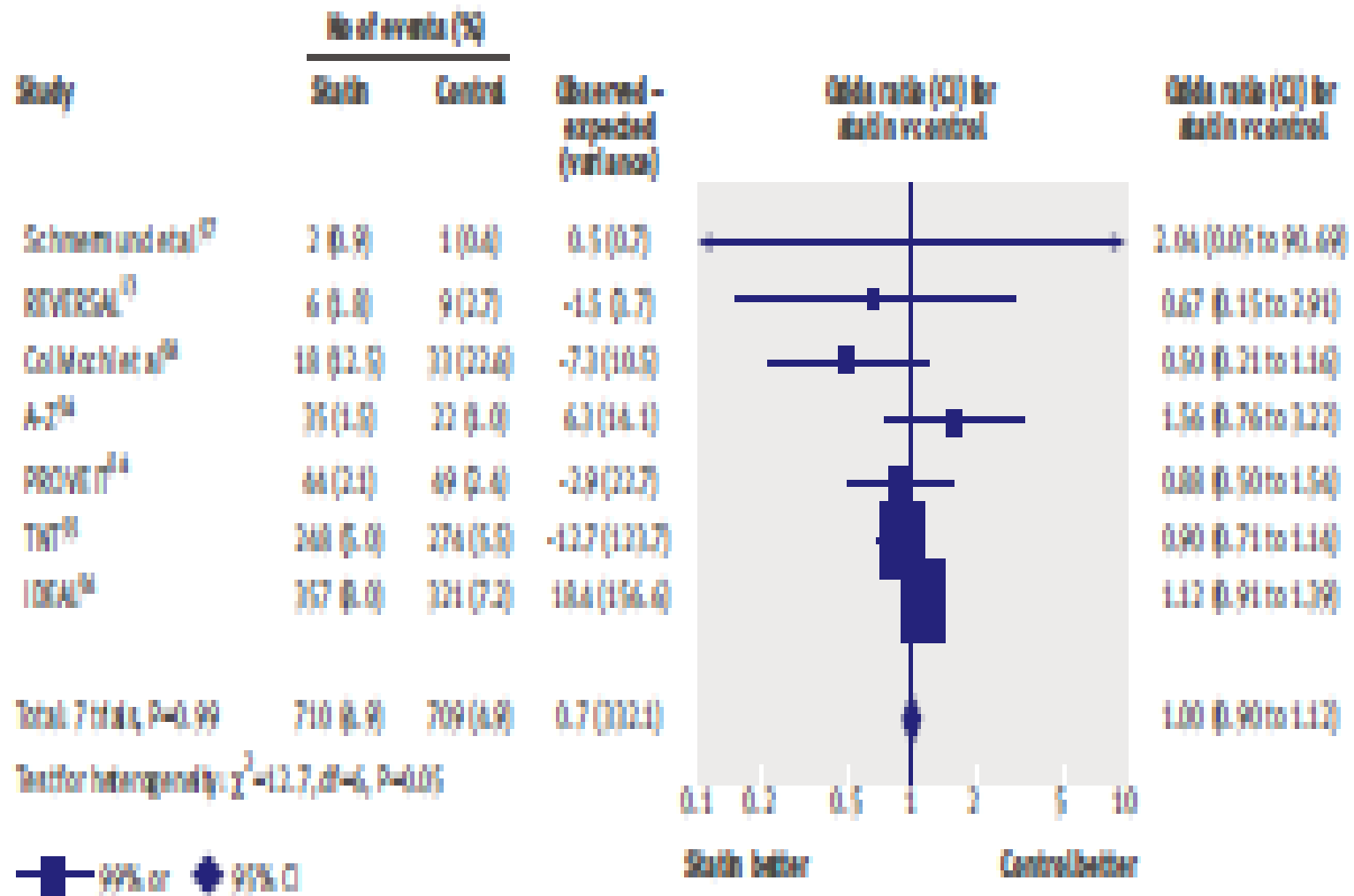


Fig 3 | Effect of statin treatment on atrial fibrillation in seven longer term trials of more intensive v standard statin regimens

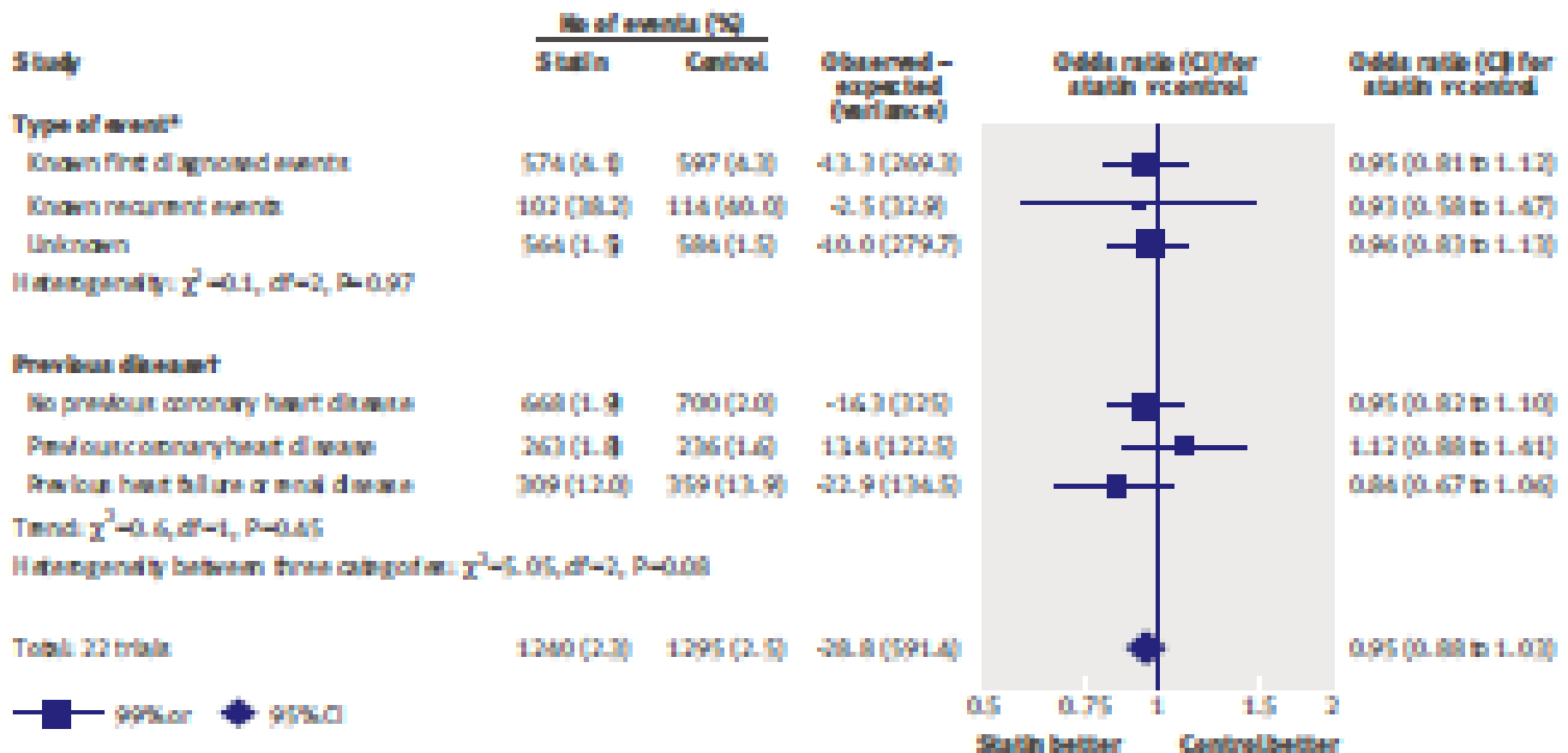


Fig 4| Effect of statin treatment on atrial fibrillation in 22 longer term trials of statin v control, by subgroups of trial population.

[†]Six trials could confirm that reported atrial fibrillation events were new (that is, incident) cases,^{1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22} and one trial²³ provided atrial fibrillation events in both those with and without history of paroxysmal atrial fibrillation at baseline. [‡]No previous coronary heart disease^{1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22}; previous coronary heart disease^{23,24,25,26,27,28,29}; previous heart failure or renal disease^{30,31,32,33}

Conclusion

- L'effet bénéfique des statines sur la FA objectivé à court terme n'est pas maintenu à long terme