Supplementary data

# Additional details concerning study assessment and selection.

Twenty-one candidate trials were identified for further assessment. [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21]

Six studies that were discarded as they were not focused on therapy with statins. [11, 12, 14, 15, 16, 17]

On further examination of these 15 remaining studies, 5 were excluded either because they did not report

any extractable data, [7, 19, 21] because of possible duplicate publication, [5] or because they were

focused on rheumatic aortic stenosis.[4]

Of the 10 studies finally selected for meta-analysis, 5 were prospective, [1, 2, 3, 10, 20], 5

retrospective, [6, 8, 9, 13, 18] whereas 3 were randomized, [1, 3, 20] and 7 not randomized, [2, 6, 8, 9, 10, 13, 18] respectively.

Finally, only three studies enrolled patients with average LDL cholesterol levels  $\leq 130 \text{ mg/dL}$ ; of these, 2 were prospective [10, 20] and one retrospective [13].

# ADDITIONAL REFERENCES

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## Legend to eFigure

eFigure 1: Meta-analysis of studies (denoted by first author and publication year) assessing the effect of statin treatment on death from any cause at follow-up (panel A, Odds Ratio and 95% confidence intervals), death from cardiovascular causes at follow-up (panel B, Odds Ratio and 95% confidence intervals), need to undergo aortic valve surgery at follow-up (panel C, Odds Ratio and 95% confidence intervals), peak aortic-jet velocity progression (panel D, mean difference and 95% confidence intervals), and aortic valve area decrease (panel E, mean difference and 95% confidence intervals), peak aortic gradient progression (panel F, mean difference and 95% confidence intervals), and on mean aortic gradient progression (panel G, mean difference and 95% confidence intervals). Squares indicating individual trial differences are scaled according to weighting in the meta-analysis. The width of the diamond for pooled data denotes the lower and upper 95% confidence intervals. Note that the x-axis of panels A-C is logarithmic.

eFigure 2: Meta-analysis of studies that enrolled patients with an LDL-cholesterol  $\leq$  130 mg/dL assessing the effect of statin treatment on aortic stenosis progression in studies: aortic valve area decrease (panel A, mean difference and 95% confidence intervals), peak aortic gradient progression (panel B, mean difference and 95% confidence intervals), and on mean aortic gradient progression (panel C, mean difference and 95% confidence intervals). Squares indicating individual trial differences are scaled according to weighting in the meta-analysis. The width of the diamond for pooled data denotes the lower and upper 95% confidence intervals.

eFigure 3: Meta-regression analysis of studies assessing the effect statin treatment duration on peak aortic-jet velocity progression over time.

eFigure 4: Meta-regression analysis of studies assessing the effect statin treatment duration on aortic valve area decrease over time.

# eFigure 1 Forest plots for the outcomes of interest by randomized and non-randomized studies

Panel A

	Statins	5	No stat	ins		Odds Ratio	Odds Ratio
Study or Subgroup	Events <sup>-</sup>	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
1.1.1 Randomized stu	idies						
SALTIRE 2005	3	77	5	78	4.9%	0.59 [0.14, 2.57]	
SEAS 2008	105	944 1 <b>021</b>	100	929 1 <b>007</b>	91.1% <b>96.0%</b>	1.04 [0.78, 1.39] 1.01 [0.76, 1.35]	<b></b>
Subtotal (95% CI)		1021	405	1007	90.0 %	1.01 [0.70, 1.35]	
Total events	108	( <b>-</b> -	105				
Heterogeneity: Chi <sup>2</sup> = (	•		,.	0%			
Test for overall effect:	Z = 0.10 (P	= 0.92)	)				
1.1.2 Non-randomized	d studies						
RAAVE 2007	1	61	4	60	4.0%	0.23 [0.03, 2.15]	←
Subtotal (95% CI)		61		60	4.0%	0.23 [0.03, 2.15]	
Total events	1		4				
Heterogeneity: Not app	olicable						
Test for overall effect:	Z = 1.28 (P	= 0.20)	)				
Total (95% CI)		1082		1067	100.0%	0.98 [0.74, 1.30]	•
Total events	109		109				
Heterogeneity: Chi <sup>2</sup> = 2	2.20, df = 2	(P = 0.3)	33); l² =	9%			
Test for overall effect:	Z = 0.12 (P	= 0.91)	)				0.1 0.2 0.5 1 2 5 10 Foreurs stating
	- (-	,	,				Favours statins Favours no statins

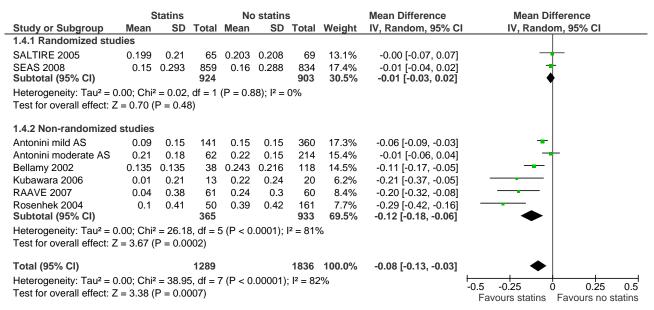
### Panel B

	Statins		No statins			Odds Ratio	Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% C	
ASTRONOMER 2010	2	134	5	135	8.0%	0.39 [0.08, 2.07]	• •	
SALTIRE 2005	3	77	3	78	4.7%	1.01 [0.20, 5.18]		
SEAS 2008	47	944	56	929	87.3%	0.82 [0.55, 1.22]		
Total (95% CI)		1155		1142	100.0%	0.79 [0.54, 1.15]	•	
Total events	52		64					
Heterogeneity: Chi <sup>2</sup> = 0.7	79, df = 2 (l	P = 0.6	67); l <sup>2</sup> = 0	%			0.1 0.2 0.5 1 2	5 10
Test for overall effect: Z	= 1.21 (P =	= 0.22)					••••••	no statins

## Panel C

	Statins		No stat	tins		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl
1.3.1 Randomized stud	ies						
ASTRONOMER 2010	28	134	27	135	8.8%	1.06 [0.58, 1.91]	
SALTIRE 2005	11	77	19	78	6.7%	0.52 [0.23, 1.18]	
SEAS 2008 Subtotal (95% CI)	267	944 <b>1155</b>	278	929 <b>1142</b>	83.3% <b>98.8%</b>	0.92 [0.76, 1.13] <b>0.91 [0.76, 1.09]</b>	<b>→</b>
Total events	306		324				
Heterogeneity: Chi <sup>2</sup> = 2.0 Test for overall effect: Z = 1.3.2 Non-randomized s	= 1.03 (P	`	,.	%			
RAAVE 2007 Subtotal (95% CI)	5	61 <b>61</b>	3	60 <b>60</b>	1.2% <b>1.2%</b>	1.70 [0.39, 7.44] 1.70 [0.39, 7.44]	
Total events Heterogeneity: Not appli	5		3				
Test for overall effect: Z		= 0.48)	1				
Total (95% CI)		1216		1202	100.0%	0.92 [0.76, 1.10]	<b></b>
Total events	311		327				
Heterogeneity: Chi <sup>2</sup> = 2.7 Test for overall effect: Z	-	`		%			0.1 0.2 0.5 1 2 5 10 Favours statins Favours no statins

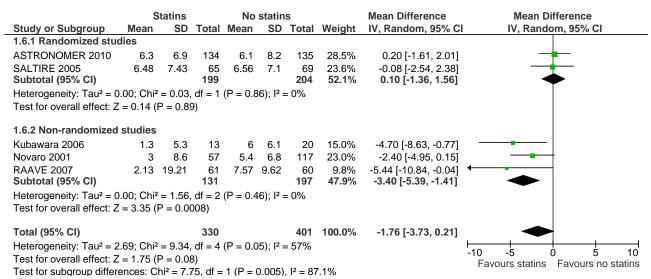
#### Panel D



#### Panel E

	Statins No st					s		Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% Cl	IV, Fixed, 95% Cl	
1.5.1 Randomized stud	lies									
ASTRONOMER 2010	0.07	0.15	134	0.08	0.21	135	12.8%	-0.01 [-0.05, 0.03]		
SALTIRE 2005	0.079	0.107	65	0.083	0.107	69	18.5%	-0.00 [-0.04, 0.03]	<b>_</b>	
SEAS 2008	0.03	0.28	859	0.03	0.28	834	34.2%	0.00 [-0.03, 0.03]	· -+-	
Subtotal (95% CI)			1058			1038	65.6%	-0.00 [-0.02, 0.02]	<b>•</b>	
Heterogeneity: Chi <sup>2</sup> = 0.	15, df =	2 (P = 0	).93); l <sup>2</sup>	= 0%						
Test for overall effect: Z	= 0.31 (	P = 0.7	5)							
1.5.2 Non-randomized	studies									
Bellamy 2002	0.04	0.15	38	0.09	0.17	118	7.6%	-0.05 [-0.11, 0.01]	+	
Mohler 2007	0.07	0.17	39	0.06	0.34	22	1.1%	0.01 [-0.14, 0.16]		
Novaro 2001	0.06	0.16	57	0.11	0.18	117	8.7%	-0.05 [-0.10, 0.00]		
RAAVE 2007	0.05	0.12	61	0.1	0.09	60	17.1%	-0.05 [-0.09, -0.01]		
Subtotal (95% CI)			195			317	34.4%	-0.05 [-0.07, -0.02]	$\bullet$	
Heterogeneity: Chi <sup>2</sup> = 0.	58, df =	3 (P = 0	).90); l²	= 0%						
Test for overall effect: Z	= 3.55 (	P = 0.0	004)							
Total (95% CI)			1253			1355	100.0%	-0.02 [-0.03, -0.00]	•	
Heterogeneity: Chi <sup>2</sup> = 7.	97, df =	6 (P = 0	).24); l <sup>2</sup>	= 25%						
Test for overall effect: Z									-0.2 -0.1 0 0.1 Favours statins Favours n	
Test for subgroup different				1 (P =	0.007),	l² = 86.	2%		Favours statills Favours II	U SIALITIS

#### Panel F



#### Panel G

	Statins No sta					S		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% C	I IV, Random, 95% CI
1.7.1 Randomized stu	dies								
ASTRONOMER 2010	3.8	4.4	134	3.9	4.9	135	24.3%	-0.10 [-1.21, 1.01]	-+-
SEAS 2008	2.7	2.9	859	2.8	2.8	834	32.5%	-0.10 [-0.37, 0.17]	<b>.</b>
Subtotal (95% CI)			993			969	56.8%	-0.10 [-0.36, 0.16]	•
Heterogeneity: Tau <sup>2</sup> = 0	0.00; Chi <sup>2</sup>	$^{2} = 0.00$	), df = 1	1 (P = 1	.00); l²	$^{2} = 0\%$			
Test for overall effect: 2	Z = 0.74 (	P = 0.4	16)						
1.7.2 Non-randomized	l studies								
Bellamy 2002	2.9	3.4	38	5.5	6.4	118	19.1%	-2.60 [-4.18, -1.02]	
Novaro 2001	2.4	7.6	57	3.3	5.1	117	13.8%	-0.90 [-3.08, 1.28]	
RAAVE 2007	2.08	8.15	61	5.06	7.17	60	10.3%	-2.98 [-5.71, -0.25]	
Subtotal (95% CI)			156			295	43.2%	-2.19 [-3.35, -1.03]	◆
Heterogeneity: Tau <sup>2</sup> = 0	0.00; Chi <sup>z</sup>	² = 1.93	3, df = 2	2 (P = 0	.38); l²	$^{2} = 0\%$			
Test for overall effect: 2	Z = 3.70 (	P = 0.0	0002)						
Total (95% CI)			1149			1264	100.0%	-0.99 [-2.04, 0.07]	•
Heterogeneity: Tau <sup>2</sup> = 0	0.88; Chi <sup>2</sup>	<sup>2</sup> = 13.7	76, df =	4 (P =	0.008)	; l <sup>2</sup> = 7 <sup>2</sup>	1%		
Test for overall effect: 2	Favours statins Favours no statins								
Test for subgroup differ	r avours statins Favours no statins								

Test for subgroup differences:  $Chi^2 = 11.84$ , df = 1 (P = 0.0006), l<sup>2</sup> = 91.6%

### eFigure 2

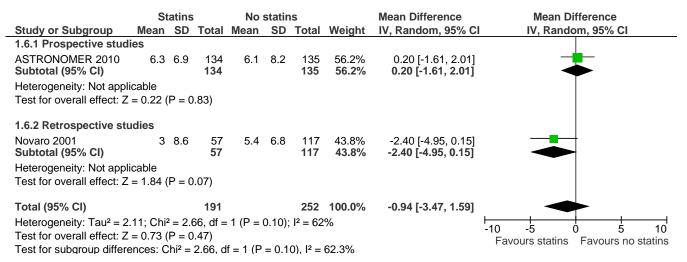
## Forest plots for the parameters of aortic stenosis progression in studies enrolling patients

### with an average cholesterol level ≤ 130 mg/dL

Panel A

	S	No	statin	S		Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% C	CI IV, Fixed, 95% CI
1.5.1 Prospective stud	lies								
ASTRONOMER 2010	0.07	0.15	134	0.08	0.21	135	56.7%	-0.01 [-0.05, 0.03]	<b>∎</b>
Mohler 2007 Subtotal (95% CI)	0.07	0.17	39 <b>173</b>	0.06	0.34	22 157		0.01 [-0.14, 0.16] -0.01 [-0.05, 0.03]	
Heterogeneity: Chi <sup>2</sup> = 0 Test for overall effect: Z				l² = 0%					
1.5.2 Retrospective st	udies								
Novaro 2001 Subtotal (95% CI)	0.06	0.16	57 <b>57</b>	0.11	0.18	117 117		-0.05 [-0.10, 0.00] -0.05 [-0.10, 0.00]	
Heterogeneity: Not app Test for overall effect: Z		P = 0.0	06)						
Total (95% CI)			230			274	100.0%	-0.02 [-0.06, 0.01]	•
Heterogeneity: Chi <sup>2</sup> = 1	.52, df =	2 (P =	0.47);	$l^2 = 0\%$					
Test for overall effect: Z Test for subgroup differ	2 = 1.46 (	P = 0.	14)			, l² = 3′	1.4%		-0.2 -0.1 0 0.1 0.2 Favours statins Favours no statins

#### Panel B

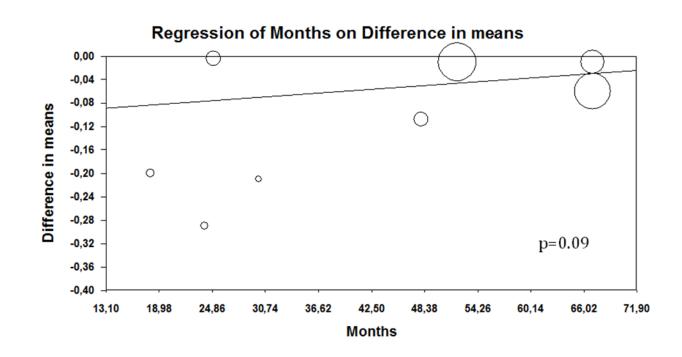


#### Panel C

	Statins			No	statin	IS		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% C	I IV, Random, 95% CI
1.7.1 Prospective stud	lies								
ASTRONOMER 2010	3.8	4.4	134	3.9	4.9	135	79.3%	-0.10 [-1.21, 1.01]	
Subtotal (95% CI)			134			135	79.3%	-0.10 [-1.21, 1.01]	<b>•</b>
Heterogeneity: Not app	licable								
Test for overall effect: Z	2 = 0.18 (	(P = 0	.86)						
1.7.2 Retrospective st	udies								
Novaro 2001	2.4	7.6	57	3.3	5.1	117	20.7%	-0.90 [-3.08, 1.28]	
Subtotal (95% CI)			57			117	20.7%	-0.90 [-3.08, 1.28]	
Heterogeneity: Not app	licable								
Test for overall effect: Z	2 = 0.81 (	(P = 0	.42)						
Total (95% CI)			191			252	100.0%	-0.27 [-1.26, 0.73]	•
Heterogeneity: Tau <sup>2</sup> = 0	-10 -5 0 5 10								
Test for overall effect: Z	-10 -5 0 5 10 Favours statins Favours no statins								
Test for subgroup differ	ences: C	chi² =	0.41, d	f = 1 (P	= 0.5	2), I² =	0%		

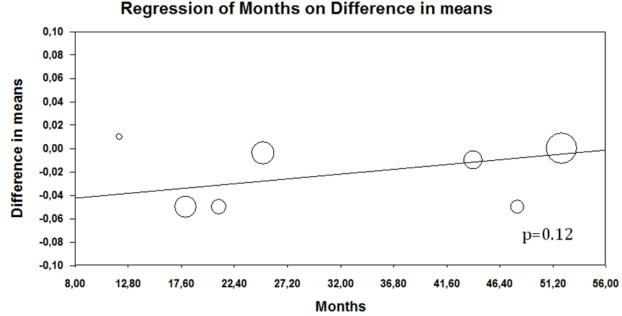
## eFigure 3

Bubble plot of the relationship between statin treatment duration and jet velocity progression across time



## eFigure 4

Bubble plot of the relationship between statin treatment duration and aortic valve area decrease across time



**Regression of Months on Difference in means**