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Statins Reduce Abdominal Aortic Aneurysm Growth, Rupture, and Perioperative Mortality: A Systematic Review and Meta-Analysis

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Background—There are no recognized pharmacological treatments for abdominal aortic aneurysms (AAA), although statins are suggested to be beneficial. We sought to summarize the literature regarding the effects of statins on human AAA growth, rupture, and 30-day mortality.

Methods and Results—We conducted a systematic review and meta-analysis of randomized and observational studies using the Cochrane CENTRAL database, MEDLINE, and EMBASE up to June 15, 2018. Review, abstraction, and quality assessment were conducted by 2 independent reviewers, and a third author resolved discrepancies. Pooled mean differences and odds ratios with 95% confidence intervals were calculated using random effects models. Heterogeneity was quantified using the I^2 statistic, and publication bias was assessed using funnel plots. Our search yielded 911 articles. One case-control and 21 cohort studies involving 80 428 patients were included. The risk of bias was low to moderate. Statin use was associated with a mean AAA growth rate reduction of 0.82 mm/y (95% confidence interval 0.33, 1.32, P=0.001, I^2=86%). Statins were also associated with a lower rupture risk (odds ratio 0.63, 95% confidence interval 0.51, 0.78, P<0.0001, I^2=27%), and preoperative statin use was associated with a lower 30-day mortality following elective AAA repair (odds ratio 0.55, 95% confidence interval 0.36, 0.83, P=0.005, I^2=57%).

Conclusions—Statin therapy may be associated with reduction in AAA progression, rupture, and lower rates of perioperative mortality following elective AAA repair. These data argue for widespread statin use in AAA patients.

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Key Words: aneurysm • meta-analysis • rupture • statin • systematic review

Abdominal aortic aneurysms (AAA) are focal dilatations of the abdominal aorta with an incidence of 3.5 to 6.5/1000 person years and a prevalence of 4% to 8%. The natural history of AAAs involves growth at 2 to 4 mm/y, and eventual rupture and death.[1] Open surgical repair of AAAs is associated with a 3% to 8% perioperative

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Clinical Perspective

What Is New?

- Statin therapy is associated with reductions in abdominal aortic aneurysm growth, rupture rate, and perioperative mortality following elective abdominal aortic aneurysm repair.

What Are the Clinical Implications?

- Healthcare providers managing patients with abdominal aortic aneurysms should consider starting statins in all such patients even in the absence of other cardiovascular indications for statin therapy.

mortality.[2] The introduction of endovascular aortic repair (EVAR) in the 1990s revolutionized the treatment of AAAs when early randomized trials demonstrated significant reductions in perioperative mortality and statistically significant reductions in operative time, blood loss, transfusion requirements, intensive care unit lengths of stay, and reductions in moderate and severe cardiopulmonary complications.[2-9] Unfortunately, the initial success of EVAR was marred with the emergence of unique complications including endograft migration, limb kinking, stenosis, occlusion, perforation, stent fracture, endoleak, and secondary rupture.[10-14] Despite endograft reengineering, EVAR is still afflicted by these complications and continues to require life-long follow-up and repetitive radiation exposure.

Unfortunately, there are no pharmacotherapies proven to attenuate the rate of progression and minimize the rupture risk of AAA. However, statins have long been regarded as candidates for this role because of their pleiotropic effects. Several studies have demonstrated that statins reduce vascular inflammation and can stimulate atherosclerotic plaque regression.[15-17] The reduction of vascular inflammation has been shown to address a key pathophysiologic collagenolytic pathway involved in AAA progression. In fact, statins have been shown in both animal and human studies to reduce collagen breakdown by stabilizing imbalances in matrix metalloproteinases (MMPs) and tissue inhibitors of matrix metalloproteinases.[18-20]

The effects of statins on AAA-related outcomes have previously been summarized.[21-33] However, only a minority of these studies[26,28,31-33] conducted meta-analyses, none of them analyzed AAA rupture risk, and considerable amounts of new data have emerged since their publication. The aims of this systematic review and meta-analysis are to summarize and mathematically synthesize the available medical literature regarding the effects of statins on AAA growth, rupture, and elective perioperative mortality.

Methods

Search Strategy and Selection Criteria

We conducted a systematic review of the medical literature according to the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement guidelines.[34] Our search strategy was devised in consultation with an experienced cardiovascular librarian. We searched the Cochrane Central Register of Controlled Clinical Trials (inception to May 2018), OVID versions of MEDLINE and MEDLINE Daily including e-publications and in-progress and nonindexed citations (inception to June 15, 2018), and EMBASE including EMBASE Classic (inception to June 15, 2018) for studies examining the effects of statins on AAA outcomes using a combination of medical subject heading terms and keywords for AAA and statins, including a list of generic statin names in order to maximize our search sensitivity. We limited our search to human studies and did not apply any language limitations. We also hand-searched the reference lists of any reviews identified by our strategy to maximize sensitivity and reduce publication bias. A detailed search strategy for all sources can be found in Data S1 and S2.

Study titles and abstracts were screened for relevance by 2 independent reviewers (K.S. and M.S.), and a third author (M.A.H.) resolved any discrepancies. We included all randomized and observational studies that assessed the effects of statin therapy on AAA growth, rupture, or elective perioperative mortality in nonruptured patients with AAA. We defined AAAs as aortas measuring >3 cm in diameter by any imaging modality. We attempted to limit our study population to adults with degenerative AAAs. Only studies reporting data on patients with a mean/median age >50 years old were included if AAA etiology was not specifically stated because the incidence of degenerative AAAs is known to begin after this age cutoff. We did not select for specific statins or dosing regimens, and no specific minimum duration of drug therapy was required. Studies reporting aneurysm growth as an outcome were included if at least 2 measurements of aneurysm size using any single imaging modality were used. We excluded case reports, case series (<30 patients), all reviews, and any other studies that did not meet our inclusion criteria.

Data Collection and Analysis

Data were collected by 2 independent abstractors (K.S. and M.S.) using a prepiloted standardized electronic data collection form, and a third author (M.A.H.) adjudicated resolution of any discrepancies. Collected variables included study authors, year of publication, design, sample size, outcomes reported, cohort demographics, and covariates as well as

study effect size measurements. Authors were contacted by e-mail correspondence for additional covariate data if not grouped by statin versus control in the original publication. Study quality and bias were assessed using the Newcastle-Ottawa Scale.[35]

We conducted a meta-analysis of the effects of statins on AAA growth, rupture, and elective perioperative mortality using published summary data and any additional summary data provided by authors. We calculated pooled mean differences and 95% confidence intervals (95% CIs) for AAA growth, and the effects of statins on AAA rupture and perioperative mortality were summarized using odds ratios (ORs) and 95% CIs. A subgroup analysis was conducted to assess the effects of statins on AAA growth by baseline AAA diameter (<4 cm versus ≥4 cm) because aneurysm growth rate is known to increase with aneurysm size, thereby implying a greater potential growth reduction benefit for larger aneurysms. In addition, perioperative mortality is known to differ considerably between open surgical repair and EVAR. Consequently, we analyzed the effect of statins on perioperative mortality following elective AAA repair by repair approach (open surgical repair versus EVAR). Because the approach to statin therapy has changed as understanding of high- versus moderate- and low-intensity treatment regimens has expanded, we also analyzed the effect of statins on AAA growth and 30-day mortality by year of study publication. We used 2007 inclusive as the cutoff because the majority of statin regimen–comparing randomized trials were published before this year.[36] Finally, we planned to conduct sensitivity analyses for each outcome, excluding any studies with a high probability of bias (Newcastle-Ottawa Scale score ≤5).

All analyses were conducted in Review Manager 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Demark) based on random-effects models, using adjusted data where available. We used the inverse-variance method for AAA growth and the generic inverse variance method for rupture and 30-day mortality to make use of adjusted-effect size estimates provided by included studies. Where unavailable, crude ORs were calculated using provided event rates. Standard deviations for meta-analysis of growth outcomes were calculated according to methods within the Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2 if they were not reported or could not be obtained.[37] The presence of publication and reporting bias was assessed visually for each outcome using funnel plots. Heterogeneity was assessed using the I^2 statistic, and significance was set at $P<0.05$. Our study protocol was registered in the International Prospective Register of Systematic Reviews before study commencement (CRD42017056480). The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Results

Search, Screening, and Full-Text Review

We identified 1225 publications using our search strategy, and a total of 911 were retained after removal of duplicates. Of the 911 articles screened, 854 were excluded and 57 passed screening. An additional 10 articles were identified by hand search of reviews identified by the search strategy, resulting in 67 articles for full-text review. Following full-text review, 45 articles were excluded for failing to report 1 of the outcomes of interest (n=12), for not comparing statins against a control group (n=10), for not studying elective AAA patients (n=10), for being abstracts without associated publications (n=7), for being clinical trial registrations without associated publication (n=2), for using duplicate data (n=3), and for being available only as a non–English language report (n=1). A total of 22 articles were included in our systematic review, and data from 21 of these were used for meta-analysis. Our search is summarized in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram in Figure 1.

Study Characteristics

Our list of included studies comprised observational studies published between 2004 and 2018. One of these studies was a case-control study, 5 were prospective cohort studies, and the remainder were retrospective cohort studies. Twelve of the included studies reported AAA growth, 5 reported or provided additional rupture rate data, and 8 reported or provided additional perioperative mortality data. The sample sizes of the included studies varied considerably for each outcome. Growth study sample sizes for the comparison of interest ranged from 121 to 2026 patients, and the follow-up ranged from 1 to 5 years. Rupture study sample sizes ranged from 121 to 7168 patients, and follow-up ranged from 1.9 to 3.6 years, although 2 studies did not report the length of follow-up. Finally, the sample size for the perioperative mortality studies ranged from 400 to 34 822 patients, and all of these studies reported 30-day mortality or a composite outcome including 30-day mortality. These characteristics are summarized in Table 1.[20,38-58]

Patient Characteristics

The overall age of patients across the studies ranged from 65 to 74 years of age, and this age distribution was similar for each of the outcomes studied. The mean ages of patients in

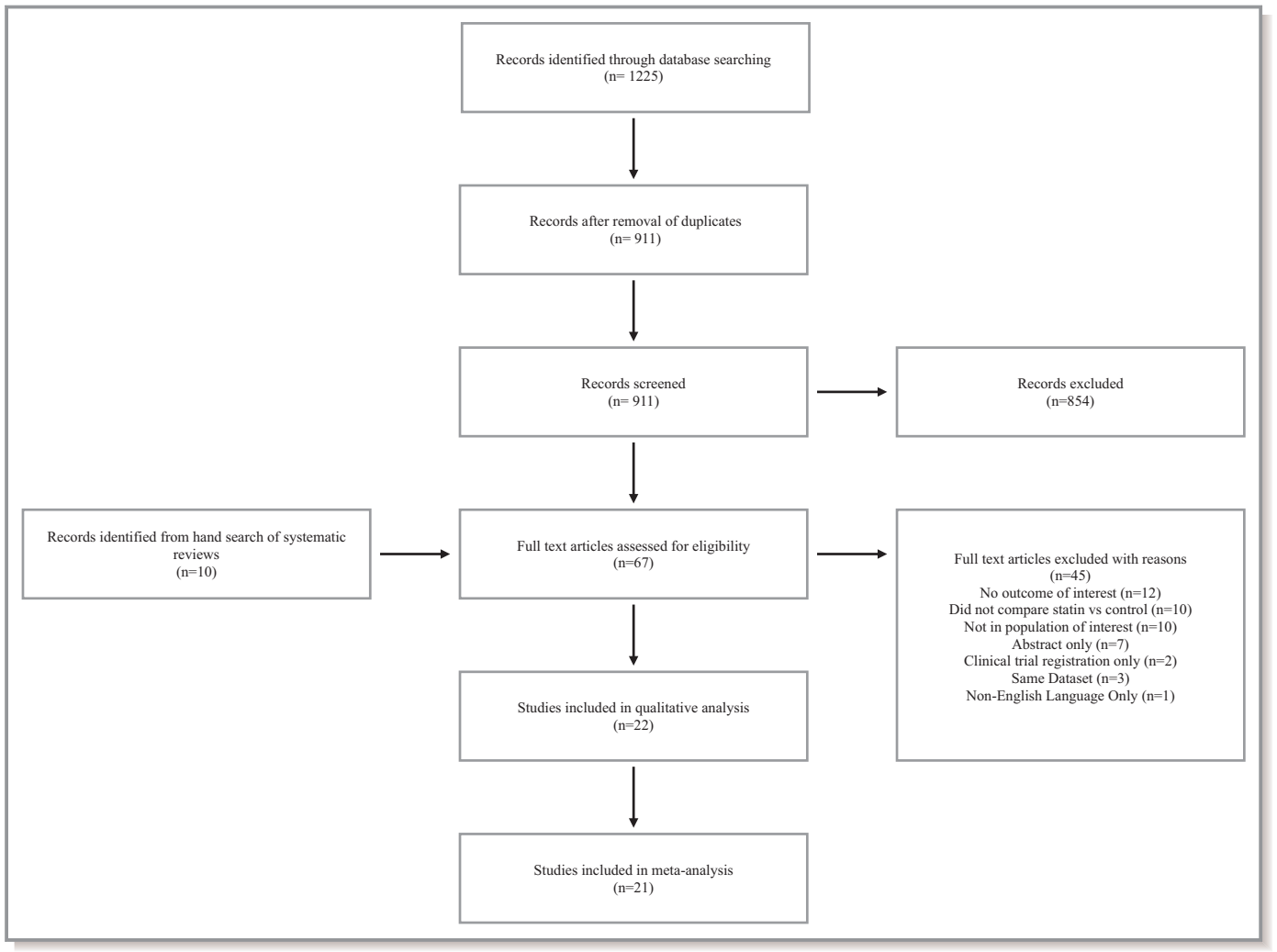

Figure 1. PRISMA study flow diagram. PRISMA indicates Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

the statin and control groups did not differ by more than 3 years in each individual study. Sex distribution varied considerably among studies, with 67% to 99% of patients being male across studies. Similarly, some individual studies demonstrated considerable differences in sex distribution between the exposure and control groups (78% versus 88% for Kertai et al[45]). Baseline AAA diameter also varied considerably across all studies and across studies reporting the same outcome. The ranges of baseline AAA diameters were 33 to 68 mm across all included studies, 33 to 46 mm for growth studies, 39 to 68 mm for rupture studies, and 46 to 59 for perioperative mortality studies. The distributions of other important covariates including hypertension, coronary artery disease, hyperlipidemia, smoking history, and diabetes mellitus also varied considerably among studies. Hypertension demonstrated a prevalence of 20% to 90% across all studies, with similar but higher frequencies in statin groups. Similarly, coronary artery disease was present in 16% to 74% of patients and generally more prevalent among statin users. The prevalence of hyperlipidemia was reported by 4 studies and ranged from 31% to 78%, with higher rates among statin users. Table 2 summarizes all available covariate data for the included studies.

Study Quality

Study quality assessment revealed an overall low (Newcastle-Ottawa Scale score ≥8) to moderate (Newcastle-Ottawa Scale score 6-7) risk of bias. The case-control study was at low risk of bias, with deduction of 1 point for poor case definition. Thirteen of the 20 cohort studies were at low risk of bias, 6 were at moderate risk of bias, and 1 was at high risk of bias. A common issue affecting quality among these studies was poor cohort comparability due to inadequate statistical control for important confounding variables (n=7). Other issues included inadequate description of the outcome assessment method (n=1), length of follow-up (n=2), and follow-up completeness/adequacy (n=2). A

Table 1. Summary of Included Studies

Author	Year	Country	Design	Sample Size*	Follos-Up (y)†	Outcome‡
Schouten; van Laanen[54]	2006	Netherlands	PC	150	3.1 median	Growth
Sukhija[55]	2006	US	RC	130	1.95	Growth
Schlosser[52]	2008	Netherlands	PC	147	3.3 median	Growth
Mosorin[49]	2008	Finland	RC	121	3.6	Growth; rupture
Karlsson[43]	2009	Sweden	RC	213	>1.5	Growth
Sweeting[56]	2010	UK	PC	1701	1.9	Growth
Thompson[57]	2010	UK	RC	1197	3.4	Growth
Ferguson[40]	2010	Australia/NZ	PC	652	5 median	Growth
Karrowni[44]	2011	US	RC	182	1	Growth
Badger[38]	2011	Ireland	RC	143	NR	Growth
van der Meij[20]	2013	Germany	RC	142	1.5	Growth
Lederle[46]	2015	US	RC	2026	3.4	Growth
Wemmelund[58]	2014	Denmark	Case-Control	7168	NR	Rupture
Gokani[42]	2015	UK	RC	983	NR	Rupture
Kertai[45]	2004	Netherlands	RC	570	NA	30-day mortality/MI
Leurs[47]	2006	Europe	PC	5892	NA	30-day mortality
Schouten; Kok[53]	2006	Netherlands	RC	500	NA	30-day mortality
McNally[48]	2010	US	RC	401	NA	30-day mortality
Nakayama[50]	2014	Japan	RC	869	1.9§	30-day mortality; growth§; rupture§
Galinanes[41]	2015	US	RC	19 323	NA	In-hospital mortality; 30-day mortality
DeMartino[39]	2016	US	RC	2963	NA	In-hospital mortality; 30-day mortality§
O'Donnell[51]	2018	US	RC	34 822	NA	30-day mortality

CC indicates Case-Control; MI, myocardial infarction; NA, not applicable; NR, not reported; PC, prospective cohort; RC, retrospective cohort.
*When data are derived from general risk factor studies, listed sample sizes are for the comparison of interest.
†Follow-up is mean for primary comparison of interest, unless otherwise indicated. Follow-up is listed as NA for studies reporting 30-days or in-hospital mortality.
‡Only outcomes of interest listed.
§From additional data provided through correspondence with authors.

summary of study quality and risk of bias assessment is presented in Table 3.

Effect of Statin Therapy on Aneurysm Growth Rate

Data from 12 of the 13 studies reporting growth outcomes were usable for meta-analysis. This included a total of 7614 patients, 2589 (34%) in the statins group compared with 5025 (66%) in the control group. Meta-analysis demonstrated that statin use was associated with a lower AAA growth rate (mean difference −0.82 mm/y, 95% CI −1.32, −0.33, P=0.001, I^2=86%) (Figure 2). Subgroup analysis by baseline AAA diameter demonstrated a greater association between statin use and AAA growth rate reduction in larger aneurysms (mean difference −1.13 mm/y, 95% CI −2.09, −0.17, P=0.02, I^2=90% versus mean difference −0.52 mm/y, 95% CI −0.98, −0.06, P=0.03, I^2=69%, for ≥4 cm versus <4 cm AAA, respectively) (Figures 3 and 4). The Badger et al[38] study was not included in the meta-analysis because annual growth rate data could not be obtained from the authors. However, their results mirrored those of our meta-analysis in that statin patients demonstrated lower mean annual AAA growth than controls (4.5% versus 7.5%, P=0.005). Analysis of the effect of study publication year on AAA growth rate demonstrated no significant association between statin therapy and AAA growth rate for studies published up to and including 2007 (mean difference −2.72 mm/y, 95% CI −6.00, 0.56, P=0.10, I^2=90%), whereas studies published after 2007 maintained a smaller but still significant association in favor of statin therapy (mean difference −0.61 mm/y, 95% CI −1.09, −0.13, P=0.01, I^2=85%). Exclusion of the Sukhija et al study[55] from meta-analysis because of low methodological quality reduced the statin effect on AAA growth rate reduction (mean difference −0.24 mm/y, 95% CI −0.40, −0.08, P=0.004, I^2=85%), but the lower effect size maintained

Table 2. Baseline Demographic and Clinical Characteristics

		Demographics		Baseline Diameter (mm)	Comorbidities/Risk Factors									Medications/Treatments						
		Age (y)	Male		HTN	DLP	CAD	CHF	CVD	Smokers	COPD	CKD/HD	DM	ACEi	ARBs	Anti-Platelets	CCB	β-Blockers	Diuretics	OSR
Schouten; van Laanen[54]	Statin	69	91	40	48	…	30	10	13	68	29	9	16	20	16	…	21	41	30	NA
	Control	69	86	37	39	…	32	5	13	72	26	2	11	29	0	…	21	32	19	NA
Sukhija[55]	Statin	67	84	46	64	…	69	…	…	28	…	…	24	75	…	97	…	77	…	NA
	Control	66	82	45	62	…	64	…	…	25	…	…	22	71	…	95	…	67	…	NA
Schlosser[52]	Cohort	65	89	39	87	69	39	…	24	40	…	25	24	…	…	…	…	…	…	NA
Mosorin[49]	Statin	71	88	39	44	…	77	…	21	24	21	…	15	14	9	…	…	71	…	NA
	Control	69	90	39	44	…	51	…	13	35	37	…	10	10	7	…	…	49	…	NA
Karlsson[43]	Cohort	71*	77	40*	59	…	31	…	14	38	6	…	4	30	…	48	…	…	…	NA
Sweeting[56]	Cohort	69	78	43	43	…	43	…	…	36	…	…	4	…	…	29	26	15	…	NA
Thompson[57]	Cohort	67	94	35	…	…	…	…	…	33	…	…	…	…	…	…	…	…	…	NA
Ferguson[40]	Statin	72	91	34*	65	…	60	…	14	89	…	…	14	43	15	65	26	35	…	NA
	Control	74	96	33*	54	…	31	…	13	83	…	…	12	30	18	45	21	19	…	NA
Karrowni[44]	Statin	70	67	41*	90	82	41	…	24	90	64	30	24	43	…	80	3	49	…	NA
	Control	69	67	41*	89	71	41	…	21	87	60	21	25	13	…	48	19	32	…	NA
Badger[38]	Cohort	59†	85	…	47	31	41	…	…	30	9	5	11	…	…	60	…	46	…	NA
van der Meij[20]	Statin	71	89	43	…	…	55	…	…	31	47	…	15	…	…	…	…	…	…	NA
	Control	69	83	42	…	…	32	…	…	51	41	…	13	…	…	…	…	…	…	NA
Lederle[46]	Cohort	71	99	40	56	…	37	…	12	26	28	7	11	41	5	…	…	41	…	NA
Wemmelund[58]	Cohort	74*	83	…	20	…	15	10	17	…	13	5	4	13	4	28	19	16	…	NA
Gokani[42]	Statin	74	85	67	70	…	42	…	11	18	…	17	12	…	…	…	…	…	…	NA
	Control	74	86	68	30	…	13	…	5	13	…	17	7	…	…	…	…	…	…	NA
Kertai[45]	Statin	65	78	…	47	…	67	5	13	30	17	10	9	43	…	35	…	64	…	100
	Control	71	88	…	49	…	36	3	16	32	30	4	5	28	…	18	…	38	…	100
Leurs[47]	Statin	70	95	58	73	…	70	…	22	24	41	18	17	…	…	…	…	…	…	0
	Control	73	94	59	63	…	59	…	17	24	43	19	12	…	…	…	…	…	…	0
Schouten; Kok[53]	Cohort	74	87	56*	42	…	33	5	15	…	25	6	10	31	…	36	31	73	17	100
McNally[48]	Statin	69	…	…	…	…	45	…	…	…	19	…	17	…	…	…	…	…	…	51
	Control	71	…	…	…	…	36	…	…	…	19	…	16	…	…	…	…	…	…	62
Nakayama[50‡]	Statin	72	78	46	75	69	57	0	15	30	1	8	30	12	40	51	56	33	9	87
	Control	74	83	49	67	34	33	0	11	30	4	12	23	7	32	26	46	18	7	83

Continued

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Table 2. Continued

		Demographics		Baseline Diameter (mm)	Comorbidities/Risk Factors								Medications/Treatments						
		Age (y)	Male		HTN	DLP	CAD	CHF	CVD	Smokers	COPD	CKD/HD	DM	ACEi	ARBs	Anti-Platelets	CCB	β-Blockers	Diuretics	OSR
Galinanes[41]	Cohort	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…	24
DeMartino[39]	Statin	70	74	58	86	…	70	8	6	91	32	5	84	21[§]	…	79	…	76	…	100
	Control	69	71	59	76	…	84	5	4	89	31	4	88	13[§]	…	53	…	62	…	100
O'Donnell[51‡]	Statin	73	81	55	87	…	34	12	…	87	32	36	22	50[§]	…	76	…	64	…	22
	Control	72	77	57	73	…	16	8	…	85	22	34	13	30[§]	…	44	…	41	…	25

All values are expressed as proportions or means for categorical and continuous variables, respectively. Missing values were not reported, could not be calculated from reported data, or authors were not able to provide the. ACEi indicates angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CAD, coronary artery disease; CCB, calcium channel blocker; CHF, congestive heart failure; CKD/HD, chronic kidney disease/dialysis; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; DLP, dyslipidemia; DM, diabetes mellitus; HTN, hypertension; NA, not available; OSR, open surgical repair.

*Indicates median.

†Age over 70 years.

‡Baseline demographics shown for entire cohort including rupture and elective cases.

§Includes ACE or ARB use.

statistical significance. All of the growth rate comparisons were affected by significant heterogeneity. A funnel plot of studies investigating the effect of statins on AAA growth rate demonstrated evidence of publication bias (Figure 5). However, the missing studies appeared to be of low quality and symmetrically distributed around the pooled effect estimate.

Effect of Statin Therapy on Aneurysm Rupture Rate

The 4 studies that reported AAA rupture rate included 9327 patients, 1486 (16%) of whom were treated with statins compared with 7841 (84%) controls. The crude rupture rate was 34% (501/1486) for statin patients and 47% (3686/7841) for control patients. Meta-analysis including available adjusted ORs demonstrated an association between statins and lower rates of AAA rupture (OR 0.63, 95% CI 0.51, 0.78, $P<0.0001$, $I^2=27\%$) (Figure 6). Heterogeneity for this comparison was low, allowing the conduct of a fixed-effects analysis that did not appreciably change the effect of statin use on AAA rupture (OR 0.67, 95% CI 0.58, 0.77, $P<0.00001$). The funnel plot for this outcome demonstrated probable publication bias of methodologically low-quality studies likely to demonstrate a smaller or no effect of statins on AAA rupture risk reduction (Figure 7).

Effect of Statin Therapy on Elective Perioperative Mortality

A total of 65 340 patients were analyzed among the 8 perioperative mortality studies. Patients taking statins comprised 59% (38 235/65 340) of this cohort, and controls accounted for 41% (27 105/65 340) of the cohort. The crude 30-day mortality rate was 1.8% (698/38 235) for the statin group and 2.6% (706/27 105) for the control group. Pooling of crude and available adjusted data demonstrated a lower perioperative mortality associated with statin use compared with controls (OR 0.64, 95% CI 0.48, 0.84, $P=0.002$, $I^2=50\%$) (Figure 8). Subgroup analysis by repair approach demonstrated a greater potential effect in the open-repair subgroup (OR 0.54, 95% CI 0.30, 1.00, $P=0.05$, $I^2=71\%$), whereas patients undergoing elective EVAR had a smaller association with lower mortality from statin use (OR 0.63, 95% CI 0.50, 0.79, $P<0.0001$, $I^2=0\%$) (Figures 9 and 10). Finally, subgroup analysis by publication year revealed statin therapy to be associated with a reduction in 30-day mortality irrespective of publication year, although studies published up to and including 2007 demonstrated a greater effect (OR 0.38, 95% CI 0.21, 0.69, $P=0.002$, $I^2=28\%$), and those published afterward demonstrated a more conservative effect (OR 0.77, 95% CI 0.64, 0.93, $P=0.008$, $I^2=19\%$). The combined elective-repair and open-repair subgroup comparisons suffered from significant and moderate heterogeneity,

Table 3. Quality Assessment of Included Studies

Case-Control Studies	Case Definition	Representativeness of Cases	Selection of Controls	Definition of Controls	Comparability of Cases and Controls	Ascertainment of Exposure	Consistent Exposure Ascertainment	Nonresponse Rate	NOS Score
Wemmelund[58]	0	1	1	1	2	1	1	1	8

Cohort Studies	Representativeness of Exposed Cohort	Selection of Nonexposed Cohort	Ascertainment of Exposure	Absence of Outcome at Start of Study	Comparability of Cohorts	Outcome Assessment	Length of Follow-Up	Adequacy of Follow-Up	
Badger[38]	1	1	1	1	0	1	0	1	6
DeMartino[39]	1	1	1	1	2	1	1	1	9
Ferguson[40]*	1	1	1	1	2	1	1	0	8
Galinanes[41]	1	1	1	1	0	1	1	1	7
Gokani[42]	1	1	1	1	2	1	1	1	9
Karlsson[43]	1	1	1	1	0	1	1	1	7
Karrowni[44]	1	1	1	1	1	1	1	1	8
Kertai[45]	1	1	1	1	2	1	0	1	8
Lederle[46]	1	1	1	1	2	1	1	1	9
Leurs[47]	1	1	1	1	2	1	1	1	9
McNally[48]	1	1	1	1	0	1	1	1	7
Mosorin[49]	1	1	1	1	2	1	1	1	9
Nakayama[50]	1	1	1	1	0	1	1	1	7
O'Donnell[51]	1	1	1	1	2	1	1	1	9
Schlosser[52]*	1	1	0	1	2	1	1	1	8
Schouten; Kok[53]	1	1	1	1	2	1	1	1	9
Schouten; van Laanen[54]*	1	1	1	1	2	1	1	1	9
Sukhija[55]	1	1	0	1	0	0	1	1	5
Sweeting[56]*	1	1	1	1	2	1	1	1	9
Thompson[57]	1	1	1	1	2	0	1	0	7
van der Meij[20]	1	1	1	1	2	1	1	1	9

Score per the Newcastle-Ottawa Scale (NOS) for the case-control and cohort studies. An NOS score ≥8 indicates low risk of bias, 6 to 7 indicates moderate risk of bias, and ≤5 indicates a high risk of bias. A maximum of 1 point is awarded per category, except for comparability of cohorts, where a maximum of 2 points can be awarded.
*Prospective Cohort study.

respectively. In contrast, the heterogeneity for the elective-EVAR subgroup was 0%, and both groups for analysis by year demonstrated low heterogeneity. Visual inspection of the funnel plot for the combined elective AAA group demonstrated likely publication bias of low- to moderate-quality negative studies, with a lower likelihood of missing low-quality studies demonstrating a protective effect of statins for 30-day mortality following elective AAA repair (Figure 11).

Discussion

Our systematic review and meta-analysis of 22 studies involving more than 80 000 patients demonstrated an association between statin use and lower AAA growth, rupture rate, and elective perioperative mortality. Furthermore, we also demonstrated a greater potential for reduction of AAA growth rate in larger AAAs, and a greater 30-day mortality rate reduction in statin users undergoing elective open AAA repair compared with those undergoing elective EVAR.

Comparison With Existing Literature

The effect of statin pharmacotherapy on AAA-related outcomes has been the subject of several previous systematic reviews dating back to 2008.[21-33] Seven of these review articles conducted meta-analyses. Two of them evaluated the effect of statin therapy on long-term survival following AAA repair,[21,22] 5 evaluated the effect of statins on AAA growth,[26,28,31-33] 1 considered the effects of cardiovascular drugs including statins on AAA rupture,[33] and 1 assessed 30-

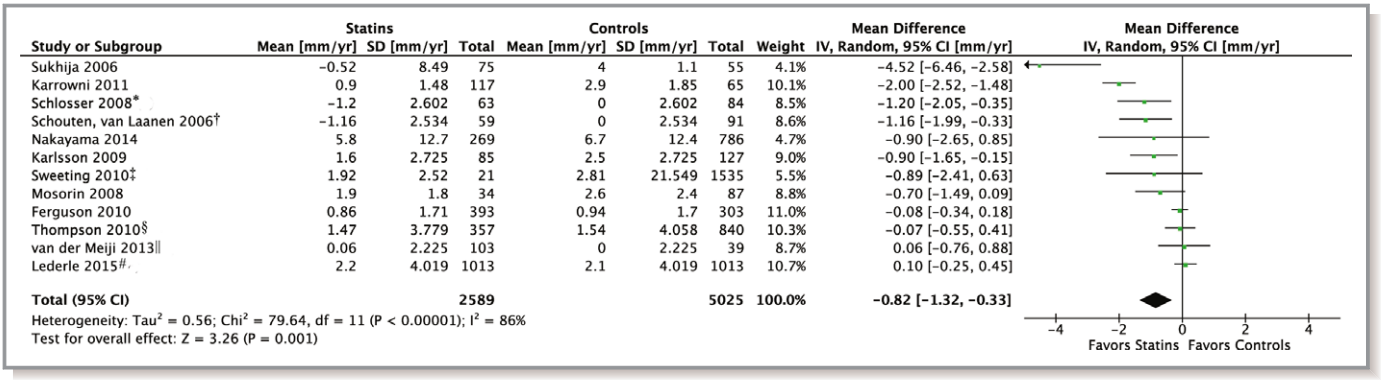

Figure 2. The effect of statin therapy on growth rate of abdominal aortic aneurysms. *Only difference provided. Control growth set as reference. Adjusted for baseline aneurysm diameter, aneurysm length, age, sex, weight, hypertension, diabetes mellitus, cerebrovascular disease, hyperlipidemia, and chronic kidney disease. †Adjusted for baseline aneurysm diameter, age, sex, diabetes mellitus, chronic obstructive pulmonary disease, claudication, nonsteroidal anti-inflammatory drugs. ‡Reduced control group size due to unavailability of medication information. Adjusted for baseline aneurysm diameter, age, sex, smoking, hypertension, coronary artery disease, diabetes mellitus, ankle-brachial index, antiplatelet medications, any antihypertensives, angiotensin-converting enzyme inhibitors, β-blockers, calcium channel blockers. §Adjusted for baseline aneurysm diameter, aneurysm curvature, sex, smoking, mean arterial pressure, antihyperglycemic medications. ‖Adjusted for baseline aneurysm diameter, age, sex, smoking, diabetes mellitus, cerebrovascular disease, cholesterol, antihypertensives, aspirin. #Adjusted for demographics, diagnoses, smoking status, drug use and dose, and healthcare utilization among many covariates. Cited sources: Sukhija 2006[55]; Karrowni 2011[44]; Schlosser 2008[52]; Schouten, van Laanen 2006[54]; Nakayama 2014[50]; Karlsson 2009[43]; Sweeting 2010[56]; Mosorin 2008[49]; Ferguson 2010[40]; Thompson 2010[57]; van der Meiji 2013[20]; Lederle 2015.[46] CI indicates confidence interval; IV, inverse variance.

day mortality following elective AAA repair.[28] Most recently, Takagi et al demonstrated that statin therapy reduced AAA growth by a standardized mean difference of 0.42 mm/y (95% CI 0.19, 0.65, $P<0.001$) in their 2012 systematic review and meta-analysis of 11 studies involving 4647 patients.[26] The results of our study are consistent with those of this and other meta-analyses of this outcome. Regarding the effect of statin therapy on AAA rupture rate, the meta-analysis of individual patient data by Sweeting et al did not demonstrate any statistically significant effect of statins or lipid lowering drugs on AAA rupture rate.[33] However, the authors noted low event rates among the included studies as well as poor reporting of cardiovascular drug use. Twine et al are responsible for the only other assessment of the effect of statin therapy on perioperative mortality following elective AAA repair.[28] They assessed 912 patients from 2 studies and demonstrated no beneficial effect of statin therapy on perioperative outcomes following AAA repair (OR 0.22, 95% CI 0.02, 2.90, $P=0.06$). However, their analysis was limited by the paucity of perioperative mortality data available at the time and was confounded by an inability to separate open and EVAR repairs. Since their study, 4 additional reports including ≈30 times more patients have been published that allowed us to arrive at our results. Furthermore, these studies reported

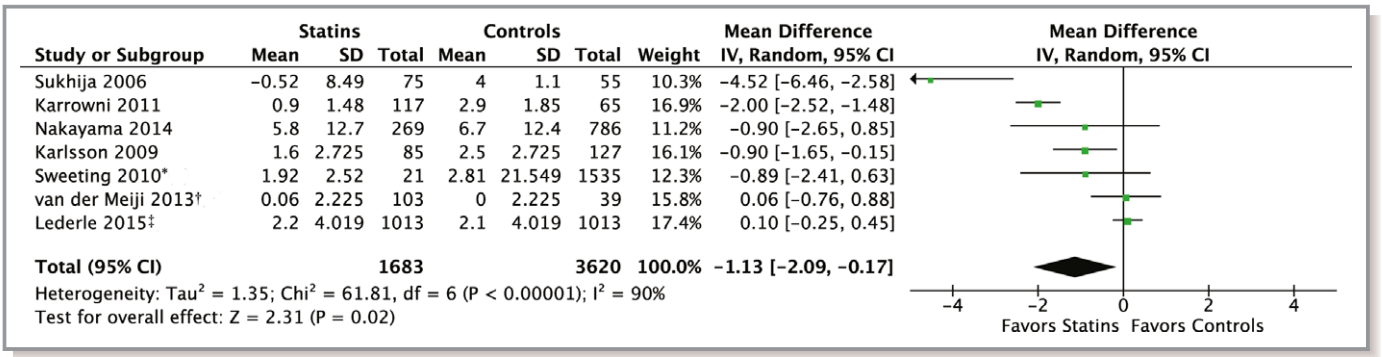

Figure 3. The effect of statin therapy on growth rate of ≥4-cm abdominal aortic aneurysms. *Only difference provided. Control growth set as reference. Adjusted for baseline aneurysm diameter, aneurysm length, age, sex, weight, hypertension, diabetes mellitus, cerebrovascular disease, hyperlipidemia, and chronic kidney disease. †Adjusted for baseline aneurysm diameter, age, sex, diabetes mellitus, chronic obstructive pulmonary disease, claudication, nonsteroidal anti-inflammatory drugs. ‡Adjusted for baseline aneurysm diameter, aneurysm curvature, sex, smoking, mean arterial pressure, antihyperglycemic medications. Cited sources: Sukhija 2006[55]; Karrowni 2011[44]; Nakayama 2014[50]; Karlsson 2009[43]; Sweeting 2010[56]; van der Meiji 2013[20]; Lederle 2015.[46] CI indicates confidence interval; IV, inverse variance.

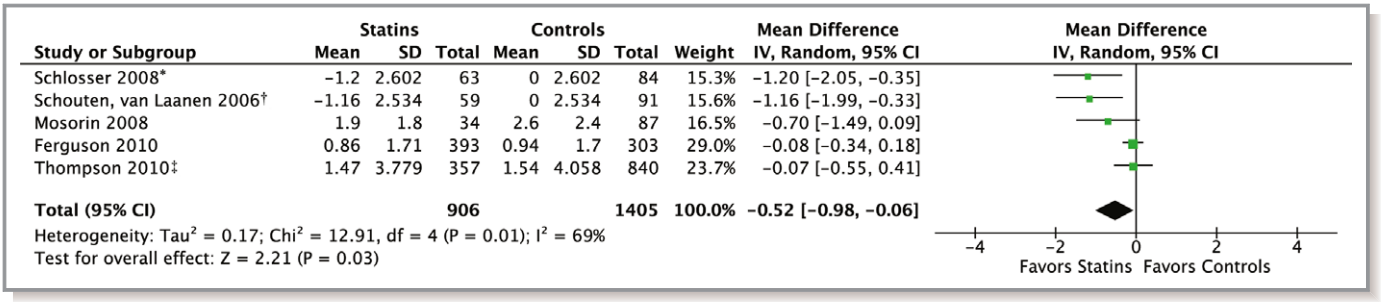

Figure 4. The effect of statin therapy on growth rate of <4 cm abdominal aortic aneurysms. *Reduced control group size due to unavailability of medication information. Adjusted for baseline aneurysm diameter, age, sex, smoking, hypertension, coronary artery disease, diabetes mellitus, ankle-brachial index, antiplatelet medications, any antihypertensives, angiotensin-converting enzyme inhibitors, β-blockers, calcium channel blockers. †Adjusted for baseline aneurysm diameter, age, sex, smoking, diabetes mellitus, cerebrovascular disease, cholesterol, antihypertensives, aspirin. ‡Adjusted for demographics, diagnoses, smoking status, drug use and dose, and healthcare utilization among many covariates. Cited sources: Schlosser 2008[52]; Schouten, van Laanen 2006[54]; Mosorin 2008[49]; Ferguson 2010[40]; Thompson 2010.[57] CI indicates confidence interval; IV, inverse variance.

proportions of repair approaches, allowing us to conduct our subgroup analyses.

Proposed Mechanisms and Explanation of Findings

The exact mechanism by which statins may attenuate AAA growth is unknown, but several theories exist. The prevailing theory is that statins reduce intramural aortic MMP expression.[59-61] Overexpression of these collagenases is thought to be an integral pathophysiologic mechanism for AAA development and progression. Culture and tissue studies have demonstrated higher levels of MMPs 1, 2, 8, 9, and 13, and lower levels of their corresponding inhibitors in aneurysmal cells and tissues and at sites of aneurysm rupture.[62-66]

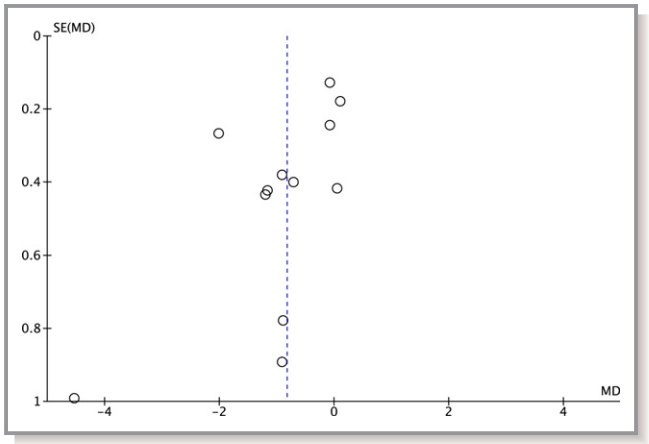

Figure 5. Funnel plot of studies investigating the effect of statins on abdominal aortic aneurysm growth. MD indicates mean growth rate difference (mm/y) with the nonstatin control group as reference; SE(MD), standard error of the mean difference.

Furthermore, correlation between degree of inflammation and MMP expression has been shown, and immunochemistry studies have localized MMP production to macrophages and B cells in the adventitia of aneurysmal aortas.[65-67] At least in part, statin-mediated MMP expression attenuation is thought to be derived from the anti-inflammatory properties of statuns.[20,59]

Aneurysm diameter and growth rate are well-established risk factors for AAA rupture, lending validity to the observed association between statin use and AAA rupture rate.[68-72] Furthermore, even though a submillimeter annual growth rate reduction is of questionable clinical significance, the association with a 37% lower rupture rate in the statin arm of our meta-analysis highlights the potential clinical importance of this effect. This small annual growth rate effect may accumulate over time to produce the observed effect on rupture rate. However, it is difficult to confidently make this assertion due to limited and incomplete reporting of follow-up in the rupture studies. An alternative explanation for the lower rupture rate among statin users may involve additional AAA stabilization by the attenuation of underlying inflammation and associated tissue friability.

The substantial perioperative mortality rate reduction that we observed in statin users compared with controls is also noteworthy. The effect that we observed in our systematic review might be attributed to the reduction of perioperative coronary events and associated complications as opposed to direct aneurysm-related causes of mortality. Multiple randomized trials have demonstrated statin-mediated reductions of cardiovascular events and mortality in primary and secondary coronary disease prevention settings.[73-76] Furthermore, studies have also shown substantial statin-mediated reductions in mortality, cardiovascular events, and adverse

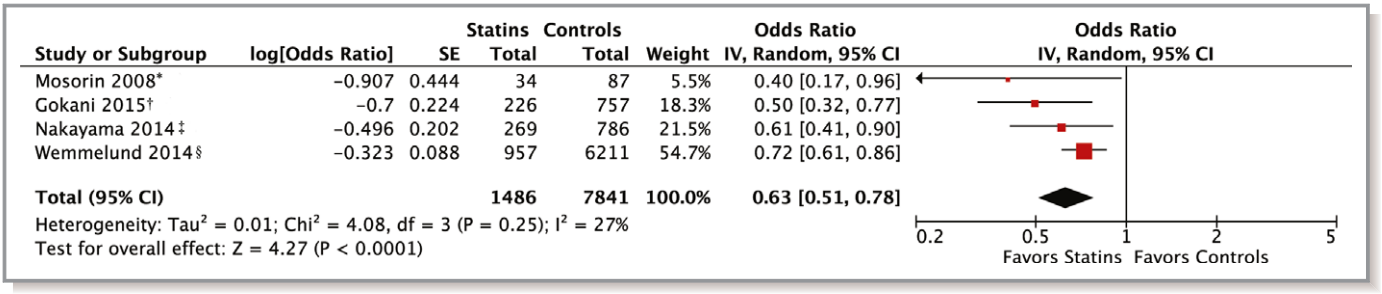

Figure 6. The effect of statin therapy on abdominal aortic aneurysm rupture risk. *Rupture or need for repair as composite. †Adjusted for age >80, sex, smoking, hypertension, diabetes mellitus, stroke, chronic kidney disease. ‡Data for this outcome provided from correspondence with authors. §Age- and sex-matched comparison between current and never/former statin use. Adjusted for hypertension, myocardial infarction, congestive heart failure, peripheral arterial disease, stroke, chronic obstructive pulmonary disease, diabetes mellitus, chronic kidney disease, antiplatelet medications, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, nonsteroidal anti-inflammatory drugs, steroids, insulin, oral antihyperglycemics, inhaled chronic obstructive pulmonary disease medications, family physician visits, marital status, gross income, smoking. Cited sources: Mosorin 2008[49]; Gokani 2015[42]; Nakayama 2014[50]; Wemmelund 2014.[58] CI indicates confidence interval; IV, inverse variance; SE, standard error.

limb events among peripheral arterial disease patients.[77] Atherosclerosis is a common underlying pathophysiologic phenomenon in coronary, peripheral, and aneurysmal disease, and multiple studies have demonstrated a high prevalence of severe coronary disease and/or peripheral artery disease among patients with AAA.[78-81] Consequently, many of these patients already have indications for statin therapy according to existing American Heart Association/American College of Cardiology guidelines.[82,83] Furthermore, the most recent Canadian Cardiovascular Society dyslipidemia guidelines consider AAA a statin-indicated condition irrespective of the presence of other cardiovascular risk factors.[84] Unfortunately, current evidence suggests that many vascular surgery patients are not adequately risk factor controlled despite knowledge of the common underlying pathophysiological mechanisms for coronary and other vascular diseases.[81,85-87] As a result, a substantial missed opportunity may exist for the reduction of mortality following both open and EVAR repair of AAA.

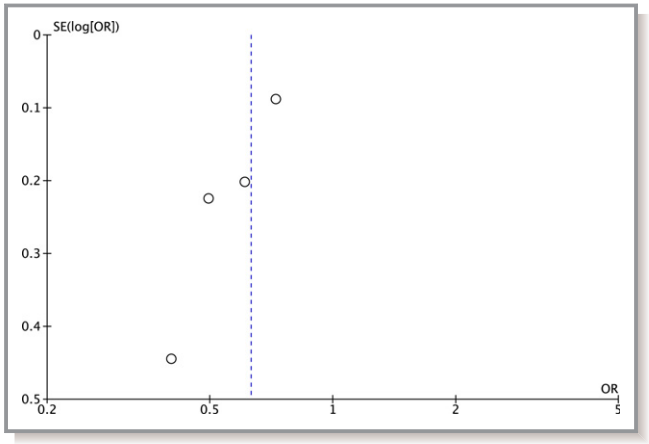

Figure 7. Funnel plot of studies investigating the effect of statins on abdominal aortic aneurysm rupture. OR indicates odds ratio for rupture with nonstatin control as reference; SE(log[OR]), standard error of the log odds ratio.

Limitations

Despite the face validity and consistency of our results with existing literature, our findings should be interpreted in light of several limitations. First, our review consisted only of observational studies. As a result, potential for propagation of information and confounding bias exists. Second, many of the comparisons that we conducted were affected by moderate to significant heterogeneity, likely reflecting the variance in covariate definitions and therefore covariate distributions among studies. The wide variation in baseline aneurysm diameter in the growth and rupture studies is likely to have significantly contributed to this heterogeneity because aneurysm growth demonstrates a progressive exponential increase in growth rate with increasing diameter. Unfortunately, due to incomplete reporting of these covariates and inability to obtain covariate information grouped by our comparison of interest, a thorough assessment of the sources of heterogeneity was not possible. Third, the relative absence of covariate data also made it difficult to precisely assess whether the pooled population represented typical patients with AAA and to what degree statins were indicated in these patients. Similarly, we were unable to account for the effects of different statins, dosages, and durations of treatment. We attempted to do so in our comparison of older and more recent studies, assuming that newer studies included greater proportions of patients on high-intensity statin regimens in response to emerging evidence and guidelines. The demonstrated potential association between statin use and AAA growth rate reduction among newer studies supported this assumption. In contrast, the

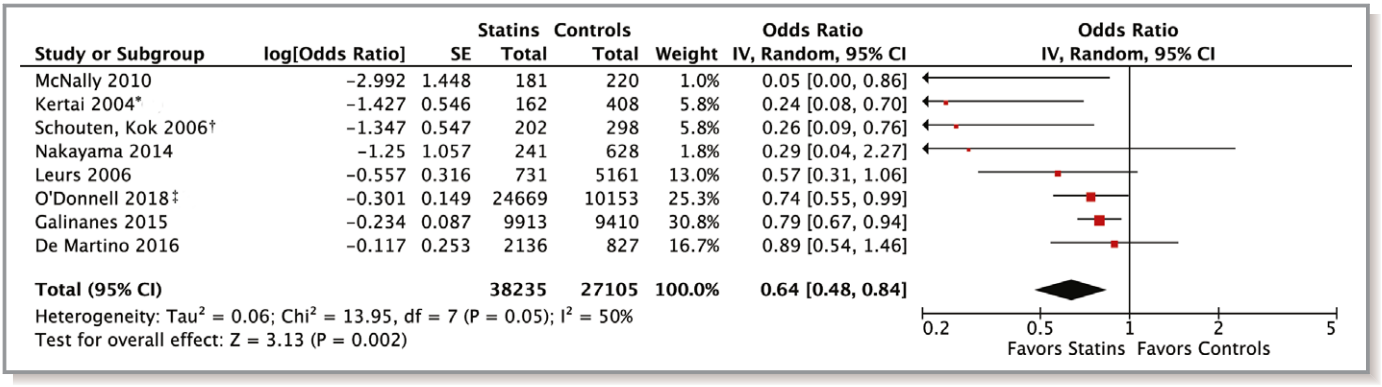

Figure 8. The effect of statin therapy on 30-day mortality following elective abdominal aortic aneurysm repair. *Outcome is composite of mortality or myocardial infarction within first of either discharge or 30 postoperative days. Adjusted for age >70, chronic obstructive pulmonary disease, revised cardiac risk index, β-blockers, propensity for β-blockers, and propensity for statins. †Adjusted for age, baseline aneurysm diameter, chronic obstructive pulmonary disease, revised cardiac risk index >2, and β-blockers. Cited sources: McNally 2010[48]; Kertai 2004[45]; Schouten, Kok 2006[53]; Nakayama 2014[50]; Leurs 2006[47]; O'Donnell 2018[51]; Galinanes 2015[41]; DeMartino 2016.[39] CI indicates confidence interval; IV, inverse variance; SE, standard error.

presence of a smaller effect of statins on perioperative mortality following AAA repair among newer studies refuted it. Therefore, our findings do not allow us to suggest specific statins, doses, or minimum duration of therapy required to achieve the suggested benefits on each AAA outcome. Finally, our study may not be an accurate assessment of all the available research. We attempted to assess the presence of publication bias for each of our main comparisons, but in many cases, the funnel plots were difficult to interpret. The limited number of studies as well as moderate to high heterogeneity precluded objective publication bias assessment using Egger and other tests and made visual interpretation of the funnel plots difficult.

Despite these limitations, conduct of a large randomized trial to confirm our findings is unlikely, and the present observational data are likely the best assessment possible of the associations between statin therapy and AAA outcomes. Due to the high prevalence of atherosclerotic disease in nonaortic vascular beds in patients with AAA and the resulting existence of indications for statin therapy by current standards, randomization of patients to statin versus placebo groups is fraught with ethical challenges. Furthermore, because statins are now generic, pharmaceutical industry funding is likely to be very difficult to secure for such a study. Finally, significant challenges exist with respect to measurement of AAA-related outcomes. Growth is commonly measured using abdominal ultrasonography due to its availability, low cost, and absent radiation exposure. However, this modality is affected by technical expertise, body habitus, bowel gas, and a number of other factors that account for the 1.6- to 4.4-mm intraobserver and up to 10-mm interobserver variability for abdominal ultrasonography of AAA.[88] Ultimately, all AAA treatments aim to reduce or prevent rupture.

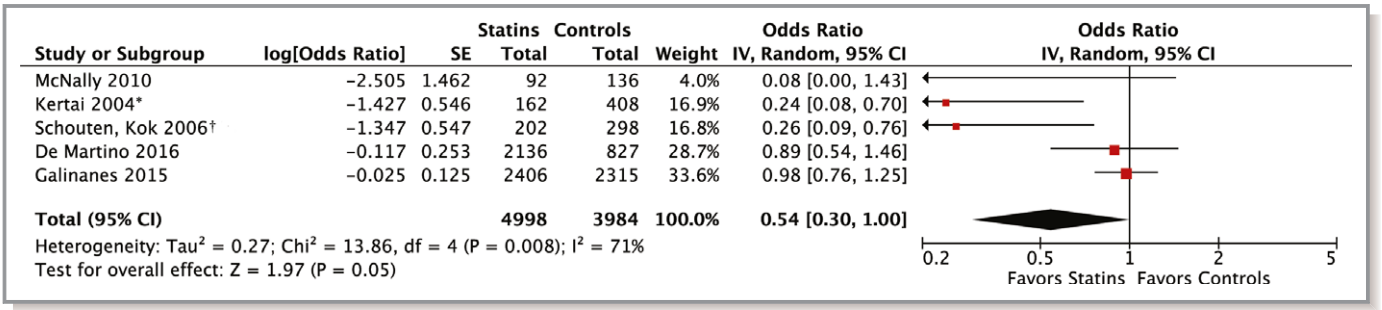

Figure 9. The effect of statin therapy on 30-day mortality following elective open abdominal aortic aneurysm repair. *Outcome is composite of mortality or myocardial infarction within first of either discharge or 30 postoperative days. Adjusted for age >70, chronic obstructive pulmonary disease, revised cardiac risk index, β-blockers, propensity for β-blockers, and propensity for statins. †Adjusted for age, baseline aneurysm diameter, chronic obstructive pulmonary disease, revised cardiac risk index >2, and β-blockers. Cited sources: McNally 2010[48]; Kertai 2004[45]; Schouten, Kok 2006[53]; DeMartino 2016[39]; Galinanes 2015.[41] CI indicates confidence interval; IV, inverse variance; SE, standard error.

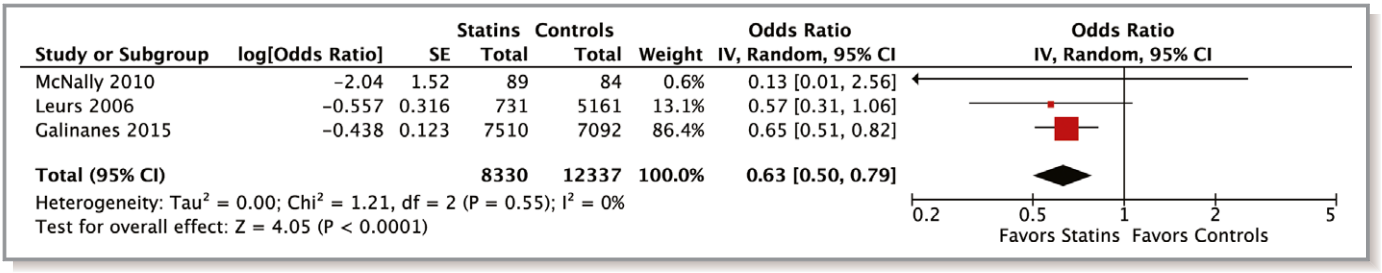

Figure 10. The effect of statin therapy on 30-day mortality following elective endovascular abdominal aortic aneurysm. Cited sources: McNally 2010[48]; Leurs 2006[47]; Galinanes 2015.[41] CI indicates confidence interval; IV, inverse variance; SE, standard error.

However, fewer than 2% of AAAs rupture below 5 cm, substantially increasing the sample size required for a randomized trial to demonstrate an effect if the standard of care is to be followed and aneurysms repaired at 5 cm for women, and 5.5 cm for men.

Conclusion

In conclusion, this systematic review and meta-analysis represents a contemporary evaluation of best available evidence on the association between statin therapy and AAA outcomes. Our analysis demonstrated a potential association among statin use and lower AAA growth, rupture, and perioperative mortality rates. Because of the magnitude and reproducibility of our findings, the high coprevalence of cardiovascular risk factors and existing indications for statin therapy in AAA patients, the low cost and relative safety of statins, as well as the significant consequences of AAA rupture and repair, physicians should consider routinely prescribing statins to all AAA patients.

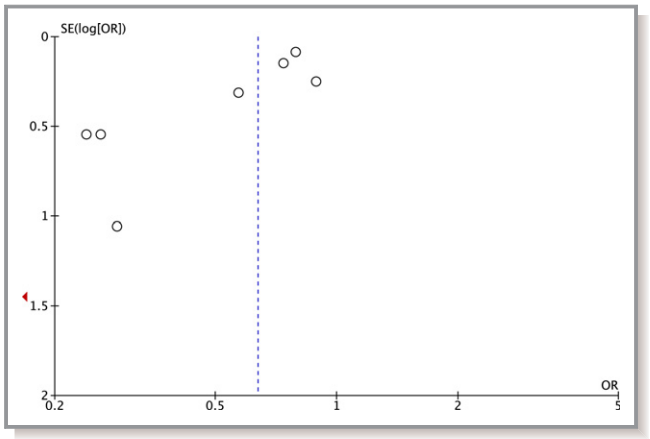

Figure 11. Funnel plot of studies investigating the effect of statins on 30-day mortality following elective abdominal aortic aneurysm repair. OR indicates odds ratio for 30-day mortality with nonstatin control as reference; SE(log[OR]), standard error of the log odds ratio.

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References

1. Powell JT, Sweeting MJ, Brown LC, Gotensparre SM, Fowkes FG, Thompson SG. Systematic review and meta-analysis of growth rates of small abdominal aortic aneurysms. *Br J Surg*. 2011;98:609–618.
2. Schermerhorn ML, O'Malley AJ, Jhaveri A, Cotterill P, Pomposelli F, Landon BE. Endovascular vs. open repair of abdominal aortic aneurysms in the Medicare population. *N Engl J Med*. 2008;358:464–474.
3. Lee WA, Carter JW, Upchurch G, Seeger JM, Huber TS. Perioperative outcomes after open and endovascular repair of intact abdominal aortic aneurysms in the United States during 2001. *J Vasc Surg*. 2004;39:491–496.
4. Lifeline Registry of EPC. Lifeline registry of endovascular aneurysm repair: long-term primary outcome measures. *J Vasc Surg*. 2005;42:1–10.
5. van Marrewijk CJ, Leurs LJ, Vallabhaneni SR, Harris PL, Buth J, Laheij RJ; EUROSTAR Collaborators. Risk-adjusted outcome analysis of endovascular abdominal aortic aneurysm repair in a large population: how do stent-grafts compare? *J Endovasc Ther*. 2005;12:417–429.
6. Giles KA, Landon BE, Cotterill P, O'Malley AJ, Pomposelli FB, Schermerhorn ML. Thirty-day mortality and late survival with reinterventions and readmissions after open and endovascular aortic aneurysm repair in Medicare beneficiaries. *J Vasc Surg*. 2011;53:6–12, 13.e1.
7. Greenhalgh RM, Brown LC, Kwong GP, Powell JT, Thompson SG; EVAR Trial Participants. Comparison of endovascular aneurysm repair with open repair in patients with abdominal aortic aneurysm (EVAR trial 1), 30-day operative mortality results: randomised controlled trial. *Lancet*. 2004;364:843–848.
8. Prinssen M, Verhoeven EL, Buth J, Cuypers PW, van Sambeek MR, Balm R, Buskens E, Grobbee DE, Blankensteijn JD; Dutch Randomized Endovascular Aneurysm Management (DREAM) Trial Group. A randomized trial comparing conventional and endovascular repair of abdominal aortic aneurysms. *N Engl J Med*. 2004;351:1607–1618.
9. Blankensteijn JD, de Jong SE, Prinssen M, van der Ham AC, Buth J, van Sterkenburg SM, Verhagen HJ, Buskens E, Grobbee DE; Dutch Randomized Endovascular Aneurysm Management (DREAM) Trial Group. Two-year outcomes after conventional or endovascular repair of abdominal aortic aneurysms. *N Engl J Med*. 2005;352:2398–2405.
10. Parent FN III, Godziachvili V, Meier GH III, Parker FM, Carter K, Gayle RG, Demasi RJ, Gregory RT. Endograft limb occlusion and stenosis after ANCURE endovascular abdominal aneurysm repair. *J Vasc Surg*. 2002;35:686–690.
11. Haider SE, Najjar SF, Cho JS, Rhee RY, Eskandari MK, Matsumura JS, Makaroun MS, Morasch MD. Sac behavior after aneurysm treatment with the Gore Excluder low-permeability aortic endoprosthesis: 12-month comparison to the original Excluder device. *J Vasc Surg*. 2006;44:694–700.
12. Criado FJ, Clark NS, McKendrick C, Longway J, Domer GS. Update on the Talent LPS AAA stent graft: results with "enhanced talent." *Semin Vasc Surg*. 2003;16:158–165.
13. Najibi S, Steinberg J, Katzen BT, Zemel G, Lin PH, Weiss VJ, Lumsden AB, Chaikof EL. Detection of isolated hook fractures 36 months after implantation of the Ancure endograft: a cautionary note. *J Vasc Surg*. 2001;34:353–356.
14. Beebe HG, Cronenwett JL, Katzen BT, Brewster DC, Green RM; Vanguard Endograft Trial Investigators. Results of an aortic endograft trial: impact of device failure beyond 12 months. *J Vasc Surg*. 2001;33:S55–S63.
15. Kleemann R, Princen HM, Emeis JJ, Jukema JW, Fontijn RD, Horrevoets AJ, Kooistra T, Havekes LM. Rosuvastatin reduces atherosclerosis development beyond and independent of its plasma cholesterol-lowering effect in APOE*3-Leiden transgenic mice: evidence for antiinflammatory effects of rosuvastatin. *Circulation*. 2003;108:1368–1374.
16. Verschuren L, Kleemann R, Offerman EH, Szalai AJ, Emeis SJ, Princen HM, Kooistra T. Effect of low dose atorvastatin versus diet-induced cholesterol lowering on atherosclerotic lesion progression and inflammation in apolipoprotein E*3-Leiden transgenic mice. *Arterioscler Thromb Vasc Biol*. 2005;25:161–167.
17. Patel TN, Shishehbor MH, Bhatt DL. A review of high-dose statin therapy: targeting cholesterol and inflammation in atherosclerosis. *Eur Heart J*. 2007;28:664–672.
18. Evans J, Powell JT, Schwalbe E, Loftus IM, Thompson MM. Simvastatin attenuates the activity of matrix metalloprotease-9 in aneurysmal aortic tissue. *Eur J Vasc Endovasc Surg*. 2007;34:302–303.
19. Steinmetz EF, Buckley C, Shames ML, Ennis TL, Vanvickle-Chavez SJ, Mao D, Goeddel LA, Hawkins CJ, Thompson RW. Treatment with simvastatin suppresses the development of experimental abdominal aortic aneurysms in normal and hypercholesterolemic mice. *Ann Surg*. 2005;241:92–101.
20. van der Meij E, Koning GG, Vriens PW, Peeters MF, Meijer CA, Kortekaas KE, Dalman RL, van Bockel JH, Hanemaaijer R, Kooistra T, Kleemann R, Lindeman JH. A clinical evaluation of statin pleiotropy: statins selectively and dose-dependently reduce vascular inflammation. *PLoS One*. 2013;8:e53882.
21. Khashram M, Williman JA, Hider PN, Jones GT, Roake JA. Management of modifiable vascular risk factors improves late survival following abdominal aortic aneurysm repair: a systematic review and meta-analysis. *Ann Vasc Surg*. 2016;22:22.
22. Zhang W, Liu Z, Liu C. Effect of lipid-modifying therapy on long-term mortality after abdominal aortic aneurysm repair: a systemic review and meta-analysis. *World J Surg*. 2015;39:794–801.
23. Kokje VBC, Hamming JF, Lindeman JHN. Editor's Choice—pharmaceutical management of small abdominal aortic aneurysms: a systematic review of the clinical evidence. *Eur J Vasc Endovasc Surg*. 2015;50:702–713.
24. Bardenhagen J, Kausch H, Wenk HH. [Factors with impact on the outcome after surgical interventions for abdominal aortic aneurysms]. *Zentralbl Chir*. 2015;140:516–524.
25. Dunne JA, Bailey MA, Griffin KJ, Sohrabi S, Coughlin PA, Scott DJ. Statins: the holy grail of abdominal aortic aneurysm (AAA) growth attenuation? A systematic review of the literature. *Curr Vasc Pharmacol*. 2014;12:168–172.
26. Takagi H, Yamamoto H, Iwata K, Goto S, Umemoto T. Effects of statin therapy on abdominal aortic aneurysm growth: a meta-analysis and meta-regression of observational comparative studies. *Eur J Vasc Endovasc Surg*. 2012;44:287–292.
27. Rughani G, Robertson L, Clarke M. Medical treatment for small abdominal aortic aneurysms. *Cochrane Database Syst Rev*. 2012:CD009536.
28. Twine CP, Williams IM. Systematic review and meta-analysis of the effects of statin therapy on abdominal aortic aneurysms. *Br J Surg*. 2011;98:346–353.
29. Bergqvist D. Pharmacological interventions to attenuate the expansion of abdominal aortic aneurysm (AAA)—a systematic review. *Eur J Vasc Endovasc Surg*. 2011;41:663–667.
30. Bailey MA, Dunne JA, Griffin KJ, Coughlin PA, Scott DJ. Systematic review and meta-analysis of the effects of statin therapy on abdominal aortic aneurysms (Br J Surg 2011; 98: 362-353). *Br J Surg*. 2011;98:744–745; author reply 745.
31. Takagi H, Matsui M, Umemoto T. A meta-analysis of clinical studies of statins for prevention of abdominal aortic aneurysm expansion. *J Vasc Surg*. 2010;52:1675–1681.
32. Guessous I, Periard D, Lorenzetti D, Cornuz J, Ghali WA. The efficacy of pharmacotherapy for decreasing the expansion rate of abdominal aortic aneurysms: a systematic review and meta-analysis. *PLoS One*. 2008;3:e1895.
33. Sweeting MJ, Thompson SG, Brown LC, Powell JT; RESCAN Collaborators. Meta-analysis of individual patient data to examine factors affecting growth and rupture of small abdominal aortic aneurysms. *Br J Surg*. 2012;99:655–665.
34. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol*. 2009;62:1006–1012.
35. Wells GA, Shea B, O' Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomised studies in meta-analyses. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed January 12, 2017.
36. Mills EJ, O'Regan C, Eyawo O, Wu P, Mills F, Berwanger O, Briel M. Intensive statin therapy compared with moderate dosing for prevention of cardiovascular events: a meta-analysis of >40 000 patients. *Eur Heart J*. 2011;32:1409–1415.
37. Higgins JP, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2* [updated September 2009]. The Cochrane Collaboration; 2008. Available at: http://www.cochrane-handbook.org/. Accessed January 12, 2017.
38. Badger SA, Jones C, McClements J, Lau LL, Young IS, Patterson CC. Surveillance strategies according to the rate of growth of small abdominal aortic aneurysms. *Vasc Med*. 2011;16:415–421.
39. De Martino RR, Beck AW, Hoel AW, Hallett JW, Arya S, Upchurch GR, Cronenwett JL, Goodney PP. Preoperative antiplatelet and statin treatment was not associated with reduced myocardial infarction after high-risk vascular operations in the Vascular Quality Initiative. *J Vasc Surg*. 2016;63:182–189.e2.
40. Ferguson CD, Clancy P, Bourke B, Walker PJ, Dear A, Buckenham T, Norman P, Golledge J. Association of statin prescription with small abdominal aortic aneurysm progression. *Am Heart J*. 2010;159:307–313.
41. Galinanes EL, Reynolds S, Dombrovskiy VY, Vogel TR. The impact of preoperative statin therapy on open and endovascular abdominal aortic aneurysm repair outcomes. *Vascular*. 2015;23:344–349.
42. Gokani VJ, Sidloff D, Bath MF, Bown MJ, Sayers RD, Choke E. A retrospective study: factors associated with the risk of abdominal aortic aneurysm rupture. *Vascul Pharmacol*. 2015;65–66:13–16.
43. Karlsson L, Bergqvist D, Lindback J, Parsson H. Expansion of small-diameter abdominal aortic aneurysms is not reflected by the release of inflammatory

mediators IL-6, MMP-9 and CRP in plasma. *Eur J Vasc Endovasc Surg*. 2009;37:420–424.

44. Karrowni W, Dughman S, Hajj GP, Miller FJ Jr. Statin therapy reduces growth of abdominal aortic aneurysms. *J Investig Med*. 2011;59:1239–1243.
45. Kertai MD, Boersma E, Westerhout CM, Klein J, van Urk H, Bax JJ, Roelandt JRTC, Poldermans D. A combination of statins and beta-blockers is independently associated with a reduction in the incidence of perioperative mortality and nonfatal myocardial infarction in patients undergoing abdominal aortic aneurysm surgery. *Eur J Vasc Endovasc Surg*. 2004;28:343–352.
46. Lederle FA, Noorbaloochi S, Nugent S, Taylor BC, Grill JP, Kohler TR, Cole L. Multicentre study of abdominal aortic aneurysm measurement and enlargement. *Br J Surg*. 2015;102:1480–1487.
47. Leurs LJ, Visser P, Laheij RJ, Buth J, Harris PL, Blankensteijn JD. Statin use is associated with reduced all-cause mortality after endovascular abdominal aortic aneurysm repair. *Vascular*. 2006;14:1–8.
48. McNally MM, Agle SC, Parker FM, Bogey WM, Powell CS, Stoner MC. Preoperative statin therapy is associated with improved outcomes and resource utilization in patients undergoing aortic aneurysm repair. *J Vasc Surg*. 2010;51:1390–1396.
49. Mosorin M, Niemela E, Heikkinen J, Lahtinen J, Tiozzo V, Satta J, Juvonen T, Biancari F. The use of statins and fate of small abdominal aortic aneurysms. *Interact Cardiovasc Thorac Surg*. 2008;7:578–581.
50. Nakayama A, Morita H, Miyata T, Hoshina K, Nagayama M, Takanashi S, Sumiyoshi T, Komuro I, Nagai R. Predictors of mortality after emergency or elective repair of abdominal aortic aneurysm in a Japanese population. *Heart Vessels*. 2014;29:65–70.
51. O'Donnell TFX, Deery SE, Shean KE, Mittleman MA, Darling JD, Eslami MH, DeMartino RR, Schermerhorn ML. Statin therapy is associated with higher long-term but not perioperative survival after abdominal aortic aneurysm repair. *J Vasc Surg*. 2018;68:392–399.
52. Schlosser FJ, Tangelder MJ, Verhagen HJ, van der Heijden GJ, Muhs BE, van der Graaf Y, Moll FL; Smart Study Group. Growth predictors and prognosis of small abdominal aortic aneurysms. *J Vasc Surg*. 2008;47:1127–1133.
53. Schouten O, Kok NFM, Hoedt MTC, van Laanen JHH, Poldermans D. The influence of aneurysm size on perioperative cardiac outcome in elective open infrarenal aortic aneurysm repair. *J Vasc Surg*. 2006; 44:435–441.
54. Schouten O, van Laanen JH, Boersma E, Vidakovic R, Feringa HH, Dunkelgrun M, Bax JJ, Koning J, van Urk H, Poldermans D. Statins are associated with a reduced infrarenal abdominal aortic aneurysm growth. *Eur J Vasc Endovasc Surg*. 2006;32:21–26.
55. Sukhija R, Aronow WS, Sandhu R, Kakar P, Babu S. Mortality and size of abdominal aortic aneurysm at long-term follow-up of patients not treated surgically and treated with and without statins. *Am J Cardiol*. 2006;97:279–280.
56. Sweeting MJ, Thompson SG, Brown LC, Greenhalgh RM, Powell JT. Use of angiotensin converting enzyme inhibitors is associated with increased growth rate of abdominal aortic aneurysms. *J Vasc Surg*. 2010;52:1–4.
57. Thompson A, Cooper JA, Fabricius M, Humphries SE, Ashton HA, Hafez H. An analysis of drug modulation of abdominal aortic aneurysm growth through 25 years of surveillance. *J Vasc Surg*. 2010;52:55–61.e2.
58. Wemmelund H, Hogh A, Hundborg HH, Thomsen RW, Johnsen SP, Lindholt JS. Statin use and rupture of abdominal aortic aneurysm. *Br J Surg*. 2014;101:966–975.
59. Yoshimura K, Nagasawa A, Kudo J, Onoda M, Morikage N, Furutani A, Aoki H, Hamano K. Inhibitory effect of statins on inflammation-related pathways in human abdominal aortic aneurysm tissue. *Int J Mol Sci*. 2015;16:11213–11228.
60. Schweitzer M, Mitmaker B, Obrand D, Sheiner N, Abraham C, Dostanic S, Meilleur M, Sugahara T, Chalifour LE. Atorvastatin modulates matrix metalloproteinase expression, activity, and signaling in abdominal aortic aneurysms. *Vasc Endovasc Surg*. 2010;44:116–122.
61. Nagashima H, Aoka Y, Sakomura Y, Sakuta A, Aomi S, Ishizuka N, Hagiwara N, Kawana M, Kasanuki H. A 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, cerivastatin, suppresses production of matrix metalloproteinase-9 in human abdominal aortic aneurysm wall. *J Vasc Surg*. 2002; 36:158–163.
62. Crowther M, Goodall S, Jones JL, Bell PR, Thompson MM. Increased matrix metalloproteinase 2 expression in vascular smooth muscle cells cultured from abdominal aortic aneurysms. *J Vasc Surg*. 2000;32:575–583.
63. Crowther M, Goodall S, Jones JL, Bell PR, Thompson MM. Localization of matrix metalloproteinase 2 within the aneurysmal and normal aortic wall. *Br J Surg*. 2000;87:1391–1400.
64. Newman KM, Jean-Claude J, Li H, Scholes JV, Ogata Y, Nagase H, Tilson MD. Cellular localization of matrix metalloproteinases in the abdominal aortic aneurysm wall. *J Vasc Surg*. 1994;20:814–820.
65. Sakalihasan N, Delvenne P, Nusgens BV, Limet R, Lapiere CM. Activated forms of MMP2 and MMP9 in abdominal aortic aneurysms. *J Vasc Surg*. 1996;24:127–133.
66. Verschuren L, Lindeman JH, van Bockel JH, Abdul-Hussien H, Kooistra T, Kleemann R. Up-regulation and coexpression of MIF and matrix metalloproteinases in human abdominal aortic aneurysms. *Antioxid Redox Signal*. 2005;7:1195–1202.
67. Nollendorfs A, Greiner TC, Nagase H, Baxter BT. The expression and localization of membrane type-1 matrix metalloproteinase in human abdominal aortic aneurysms. *J Vasc Surg*. 2001;34:316–322.
68. Szilagyi DE, Smith RF, DeRusso FJ, Elliott JP, Sherrin FW. Contribution of abdominal aortic aneurysmectomy to prolongation of life. *Ann Surg*. 1966;164:678–699.
69. Reed WW, Hallett JW Jr, Damiano MA, Ballard DJ. Learning from the last ultrasound. A population-based study of patients with abdominal aortic aneurysm. *Arch Intern Med*. 1997;157:2064–2068.
70. Limet R, Sakalihassan N, Albert A. Determination of the expansion rate and incidence of rupture of abdominal aortic aneurysms. *J Vasc Surg*. 1991;14:540–548.
71. Guirguis EM, Barber GG. The natural history of abdominal aortic aneurysms. *Am J Surg*. 1991;162:481–483.
72. Brown LC, Powell JT. Risk factors for aneurysm rupture in patients kept under ultrasound surveillance. UK Small Aneurysm Trial Participants. *Ann Surg*. 1999;230:289–296; discussion 296-297.
73. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ; JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008;359:2195–2207.
74. Yusuf S, Bosch J, Dagenais G, Zhu J, Xavier D, Liu L, Pais P, Lopez-Jaramillo P, Leiter LA, Dans A, Avezum A, Piegas LS, Parkhomenko A, Keltai K, Keltai M, Sliwa K, Peters RJ, Held C, Chazova I, Yusoff K, Lewis BS, Jansky P, Khunti K, Toff WD, Reid CM, Varigos J, Sanchez-Vallejo G, McKelvie R, Pogue J, Jung H, Gao P, Diaz R, Lonn E; HOPE-3 Investigators. Cholesterol lowering in intermediate-risk persons without cardiovascular disease. *N Engl J Med*. 2016;374:2021–2031.
75. Deedwania P, Barter P, Carmena R, Fruchart JC, Grundy SM, Haffner S, Kastelein JJ, LaRosa JC, Schachner H, Shepherd J, Waters DD; Treating to New Targets Investigators. Reduction of low-density lipoprotein cholesterol in patients with coronary heart disease and metabolic syndrome: analysis of the Treating to New Targets study. *Lancet*. 2006;368:919–928.
76. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344:1383–1389.
77. Kumbhani DJ, Steg PG, Cannon CP, Eagle KA, Smith SC Jr, Goto S, Ohman EM, Elbez Y, Sritara P, Baumgartner I, Banerjee S, Creager MA, Bhatt DL; REACH Registry Investigators. Statin therapy and long-term adverse limb outcomes in patients with peripheral artery disease: insights from the REACH registry. *Eur Heart J*. 2014;35:2864–2872.
78. Vanni V, Turtiainen J, Hakala T, Salenius J, Suominen V, Oksala N, Hernesniemi J. Vascular comorbidities and demographics of patients with ruptured abdominal aortic aneurysms. *Surgery*. 2016;159:1191–1198.
79. Elkalioubie A, Haulon S, Duhamel A, Rosa M, Rauch A, Staels B, Susen S, Van Belle E, Dupont A. Meta-analysis of abdominal aortic aneurysm in patients with coronary artery disease. *Am J Cardiol*. 2015;116:1451–1456.
80. Durieux R, Van Damme H, Labropoulos N, Yazici A, Legrand V, Albert A, Defraigne JO, Sakalihasan N. High prevalence of abdominal aortic aneurysm in patients with three-vessel coronary artery disease. *Eur J Vasc Endovasc Surg*. 2014;47:273–278.
81. Baumgartner I, Hirsch AT, Abola MT, Cacoub PP, Poldermans D, Steg PG, Creager MA, Bhatt DL; REACH Registry Investigators. Cardiovascular risk profile and outcome of patients with abdominal aortic aneurysm in outpatients with atherothrombosis: data from the Reduction of Atherothrombosis for Continued Health (REACH) Registry. *J Vasc Surg*. 2008;48:808–814.
82. Gerhard-Herman MD, Gornik HL, Barrett C, Barshes NR, Corriere MA, Drachman DE, Fleisher LA, Fowkes FG, Hamburg NM, Kinlay S, Lookstein R, Misra S, Mureebe L, Olin JW, Patel RA, Regensteiner JG, Schanzer A, Shishehbor MH, Stewart KJ, Treat-Jacobson D, Walsh ME. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2017;69:e71–e126.
83. Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Guyton RA, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Rooke TW, Hirsch AT, Misra S, Sidawy AN, Beckman JA, Findeiss LK, Golzarian J, Gornik HL, Jaff MR, Moneta GL, Olin JW, Stanley JC, White CJ, White

JV, Zierler RE, Haskal ZJ, Hertzer NR, Bakal CW, Creager MA, Hiratzka LF, Murphy WRC, Puschett JB, Rosenfield KA, Sacks D, Taylor LM Jr, White RA. Management of patients with peripheral artery disease (compilation of 2005 and 2011 ACCF/AHA guideline recommendations): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;127:1425–1443.

84. Anderson TJ, Gregoire J, Pearson GJ, Barry AR, Couture P, Dawes M, Francis GA, Genest J Jr, Grover S, Gupta M, Hegele RA, Lau DC, Leiter LA, Lonn E, Mancini GB, McPherson R, Ngui D, Poirier P, Sievenpiper JL, Stone JA, Thanassoulis G, Ward R. 2016 Canadian Cardiovascular Society guidelines for the management of dyslipidemia for the prevention of cardiovascular disease in the adult. *Can J Cardiol*. 2016;32:1263–1282.
85. Kurzencwyg D, Filion KB, Pilote L, Nault P, Platt RW, Rahme E, Steinmetz O, Eisenberg MJ. Cardiac medical therapy among patients undergoing abdominal aortic aneurysm repair. *Ann Vasc Surg*. 2006;20:569–576.
86. Sharma S, Thapa R, Jeevanantham V, Myers T, Hu C, Brimacombe M, Vacek JL, Dawn B, Gupta K. Comparison of lipid management in patients with coronary versus peripheral arterial disease. *Am J Cardiol*. 2014;113:1320–1325.
87. Berger JS, Ladapo JA. Underuse of prevention and lifestyle counseling in patients with peripheral artery disease. *J Am Coll Cardiol*. 2017;69:2293–2300.
88. Beales L, Wolstenhulme S, Evans JA, West R, Scott DJ. Reproducibility of ultrasound measurement of the abdominal aorta. *Br J Surg*. 2011;98:1517–1525.

SUPPLEMENTAL MATERIAL

Data S1.

Original literature search strategy

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <January 2017>

Search Strategy:

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1 Aortic Aneurysm, Abdominal/ (430)

2 abdominal aort* aneurysm*.tw,hw. (657)

3 AAA.tw,hw. (356)

4 AAAs.tw,hw. (76)

5 1 or 2 or 3 or 4 (817)

6 exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/ (4050)

7 (hydroxymethylglutaryl CoA adj4 inhibitor*).tw,hw. (2848)

8 (HMG-CoA adj5 inhibitor*).tw,hw. (640)

9 (hydroxymethylglutaryl-Coenzyme A adj5 Inhibitor*).tw,hw. (1894)

10 (hydroxymethylglutaryl-Co-enzyme A adj5 Inhibitor*).tw,hw. (0)

11 statin*.tw,hw. (4943)

12 lipid-lowering.tw,hw. (2441)

13 Atorvastatin Calcium/ (1457)

14 atorvastatin.tw,hw. (3282)

15 Lipitor.tw,hw. (22)

16 fluvastatin.tw,hw. (508)

17 fluindostatin.tw,hw. (195)

18 Lescol.tw,hw. (47)

19 exp Lovastatin/ (1558)

20 lovastatin.tw,hw. (763)

21 mevinolin.tw,hw. (166)

22 Mevacor.tw,hw. (9)

23 Altoprev.tw,hw. (0)

24 simvastatin.tw,hw. (2518)

25 Zocor.tw,hw. (32)

26 Pravastatin/ (855)

27 pravastatin.tw,hw. (1506)

28 Pravachol.tw,hw. (5)

29 Rosuvastatin Calcium/ (521)

30 rosuvastatin.tw,hw. (1259)

31 Crestor.tw,hw. (12)

32 pitavastatin.tw,hw. (223)

33 Livalo.tw,hw. (1)

34 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 18 or 19 or 20 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 (11596)

35 5 and 34 (21)

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Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R)

Search Strategy:

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1 Aortic Aneurysm, Abdominal/ (16098)

2 abdominal aort* aneurysm*.tw,kf. (15678)

3 AAA.tw,kf. (10962)

4 AAAs.tw,kf. (2779)

5 1 or 2 or 3 or 4 (26494)

6 exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/ (34312)

7 (hydroxymethylglutaryl CoA adj4 inhibitor*).tw,kf. (277)

8 (HMG-CoA adj5 inhibitor*).tw,kf. (4435)

9 (hydroxymethylglutaryl-Coenzyme A adj5 Inhibitor*).tw,kf. (421)

10 (hydroxymethylglutaryl-Co-enzyme A adj5 Inhibitor*).tw,kf. (5)

11 statin*.tw,kf. (35058)

12 lipid-lowering.tw,kf. (12534)

13 Atorvastatin Calcium/ (5655)

14 atorvastatin.tw,kf. (7046)

15 Lipitor.tw,kf. (167)

16 fluvastatin.tw,kf. (1677)

17 fluindostatin.tw,kf. (4)

18 Lescol.tw,kf. (79)

19 exp Lovastatin/ (10045)

20 lovastatin.tw,kf. (3482)

21 mevinolin.tw,kf. (399)

22 Mevacor.tw,kf. (46)

23 Altoprev.tw,kf. (2)

24 simvastatin.tw,kf. (8124)

25 Zocor.tw,kf. (107)

26 Pravastatin/ (3257)

27 pravastatin.tw,kf. (3778)

28 Pravachol.tw,kf. (23)

29 Rosuvastatin Calcium/ (2006)

30 rosuvastatin.tw,kf. (2702)

31 Crestor.tw,kf. (51)

32 pitavastatin.tw,kf. (696)

33 Livalo.tw,kf. (15)

34 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 18 or 19 or 20 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 (61205)

35 5 and 34 (268)

36 remove duplicates from 35 (263)

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Database: Embase Classic+Embase <1947 to 2017 February 24>

Search Strategy:

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1 abdominal aorta aneurysm/ (24624)

2 abdominal aort* aneurysm*.tw,kw. (20079)

3 (AAA or AAAs).tw,kw. (15213)

4 1 or 2 or 3 (33996)

5 exp hydroxymethylglutaryl coenzyme A reductase inhibitor/ (122470)

6 (hydroxymethylglutaryl CoA adj4 inhibitor*).tw,kw. (537)

7 (HMG-CoA adj5 inhibitor*).tw,kw. (6598)

8 (hydroxymethylglutaryl-Coenzyme A adj5 Inhibitor*).tw,kw. (504)

9 (hydroxymethylglutaryl-Co-enzyme A adj5 Inhibitor*).tw,kw. (3)

10 statin*.tw,kw. (56902)

11 lipid-lowering.tw,kw. (18268)

12 atorvastatin.tw,kw. (11621)

13 Lipitor.tw,kw. (1945)

14 fluvastatin.tw,kw. (2440)

15 fluindostatin.tw,kw. (6)

16 Lescol.tw,kw. (709)

17 lovastatin.tw,kw. (4660)

18 mevinolin.tw,kw. (499)

19 mevacor.tw,kw. (801)

20 altoprev.tw,kw. (54)

21 simvastatin.tw,kw. (12516)

22 Zocor.tw,kw. (1914)

23 pravastatin.tw,kw. (5280)

24 Pravachol.tw,kw. (636)

25 rosuvastatin.tw,kw. (4806)

26 Crestor.tw,kw. (856)

27 pitavastatin.tw,kw. (1228)

28 Livalo.tw,kw. (136)

29 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 (144720)

30 4 and 29 (846)

Data S2.

Search strategy for updated literature search

Database: All Ovid Medline <1946 - present>

Search Strategy:

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1 Aortic Aneurysm, Abdominal/ (17204)

2 abdominal aort* aneurysm*.tw,kf. (16782)

3 AAA.tw,kf. (11967)

4 AAAs.tw,kf. (2948)

5 1 or 2 or 3 or 4 (28250)

6 exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/ (36492)

7 (hydroxymethylglutaryl CoA adj4 inhibitor*).tw,kf. (346)

8 (HMG-CoA adj5 inhibitor*).tw,kf. (4548)

9 (hydroxymethylglutaryl-Coenzyme A adj5 Inhibitor*).tw,kf. (423)

10 (hydroxymethylglutaryl-Co-enzyme A adj5 Inhibitor*).tw,kf. (6)

11 statin*.tw,kf. (38162)

12 lipid-lowering.tw,kf. (13408)

13 Atorvastatin Calcium/ (5950)

14 atorvastatin.tw,kf. (7603)

15 Lipitor.tw,kf. (181)

16 fluvastatin.tw,kf. (1752)

17 fluindostatin.tw,kf. (4)

18 Lescol.tw,kf. (79)

19 exp Lovastatin/ (10410)

20 lovastatin.tw,kf. (3602)

21 mevinolin.tw,kf. (399)

22 Mevacor.tw,kf. (47)

23 Altoprev.tw,kf. (2)

24 simvastatin.tw,kf. (8604)

25 Zocor.tw,kf. (109)

26 Pravastatin/ (3309)

27 pravastatin.tw,kf. (3884)

28 Pravachol.tw,kf. (23)

29 Rosuvastatin Calcium/ (2171)

30 rosuvastatin.tw,kf. (3012)

31 Crestor.tw,kf. (58)

32 pitavastatin.tw,kf. (779)

33 Livalo.tw,kf. (16)

34 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 18 or 19 or 20 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 (65755)

35 5 and 34 (298)

36 remove duplicates from 35 (295)

37 limit 36 to ed=20170201-20180615 (27)

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Database: EBM Reviews - Cochrane Central Register of Controlled Trials <May 2018>

Search Strategy:

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1 Aortic Aneurysm, Abdominal/ (504)

2 abdominal aort* aneurysm*.tw,hw. (850)

3 AAA.tw,hw. (500)

4 AAAs.tw,hw. (107)

5 1 or 2 or 3 or 4 (1086)

6 exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/ (4774)

7 (hydroxymethylglutaryl CoA adj4 inhibitor*).tw,hw. (3210)

8 (HMG-CoA adj5 inhibitor*).tw,hw. (695)

9 (hydroxymethylglutaryl-Coenzyme A adj5 Inhibitor*).tw,hw. (2703)

10 (hydroxymethylglutaryl-Co-enzyme A adj5 Inhibitor*).tw,hw. (0)

11 statin*.tw,hw. (6731)

12 lipid-lowering.tw,hw. (2972)

13 Atorvastatin Calcium/ (2005)

14 atorvastatin.tw,hw. (4233)

15 Lipitor.tw,hw. (67)

16 fluvastatin.tw,hw. (558)

17 fluindostatin.tw,hw. (224)

18 Lescol.tw,hw. (48)

19 exp Lovastatin/ (1913)

20 lovastatin.tw,hw. (809)

21 mevinolin.tw,hw. (199)

22 Mevacor.tw,hw. (12)

23 Altoprev.tw,hw. (0)

24 simvastatin.tw,hw. (3106)

25 Zocor.tw,hw. (40)

26 Pravastatin/ (954)

27 pravastatin.tw,hw. (1698)

28 Pravachol.tw,hw. (14)

29 Rosuvastatin Calcium/ (869)

30 rosuvastatin.tw,hw. (1835)

31 Crestor.tw,hw. (31)

32 pitavastatin.tw,hw. (326)

33 Livalo.tw,hw. (9)

34 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 18 or 19 or 20 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 (15037)

35 5 and 34 (30)

36 limit 35 to up=201702-201806 (27)

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Database: Embase Classic+Embase <1947 to 2018 June 14>

Search Strategy:

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1 abdominal aorta aneurysm/ (23828)

2 abdominal aort* aneurysm*.tw,kw. (21653)

3 (AAA or AAAs).tw,kw. (16809)

4 1 or 2 or 3 (36260)

5 exp hydroxymethylglutaryl coenzyme A reductase inhibitor/ (130250)

6 (hydroxymethylglutaryl CoA adj4 inhibitor*).tw,kw. (589)

7 (HMG-CoA adj5 inhibitor*).tw,kw. (6798)

8 (hydroxymethylglutaryl-Coenzyme A adj5 Inhibitor*).tw,kw. (511)

9 (hydroxymethylglutaryl-Co-enzyme A adj5 Inhibitor*).tw,kw. (4)

10 statin*.tw,kw. (63210)

11 lipid-lowering.tw,kw. (19884)

12 atorvastatin.tw,kw. (12733)

13 Lipitor.tw,kw. (2014)

14 fluvastatin.tw,kw. (2543)

15 fluindostatin.tw,kw. (6)

16 Lescol.tw,kw. (714)

17 lovastatin.tw,kw. (4864)

18 mevinolin.tw,kw. (498)

19 mevacor.tw,kw. (809)

20 altoprev.tw,kw. (51)

21 simvastatin.tw,kw. (13360)

22 Zocor.tw,kw. (1940)

23 pravastatin.tw,kw. (5522)

24 Pravachol.tw,kw. (640)

25 rosuvastatin.tw,kw. (5375)

26 Crestor.tw,kw. (892)

27 pitavastatin.tw,kw. (1348)

28 Livalo.tw,kw. (147)

29 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 (156327)

30 4 and 29 (890)

31 limit 30 to dd=20170201-20180615 (41)