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What proportion of symptomatic side effects in patients taking statins are genuinely caused by the drug? Systematic review of randomized placebo-controlled trials to aid individual patient choice

Judith A Finegold[1], Charlotte H Manisty[1], Ben Goldacre[2], Anthony J Barron[1] and Darrel P Francis[1]

Abstract

Objective: Discussions about statin efficacy in cardiovascular prevention are always based on data from blinded randomized controlled trials (RCTs) comparing statin to placebo; however, discussion of side effects is not. Clinicians often assume symptoms occurring with statins are caused by statins, encouraging discontinuation. We test this assumption and calculate an evidence-based estimate of the probability of a symptom being genuinely attributable to the statin itself.

Methods: We identified RCTs comparing statin to placebo for cardiovascular prevention that reported side effects separately in the two arms.

Results: Among 14 primary prevention trials (46,262 participants), statin therapy increased diabetes by absolute risk of 0.5% (95% CI 0.1–1%, $p = 0.012$), meanwhile reducing death by a similar extent: −0.5% (−0.9 to −0.2%, $p = 0.003$). In the 15 secondary prevention RCTs (37,618 participants), statins decreased death by 1.4% (−2.1 to −0.7%, $p < 0.001$). There were no other statin-attributable symptoms, although asymptomatic liver transaminase elevation was 0.4% more frequent with statins across all trials. Serious adverse events and withdrawals were similar in both arms.

Conclusions: Only a small minority of symptoms reported on statins are genuinely due to the statins: almost all would occur just as frequently on placebo. Only development of new-onset diabetes mellitus was significantly higher on statins than placebo; nevertheless only 1 in 5 of new cases were actually caused by statins. Higher statin doses produce a detectable effect, but even still the proportion attributable to statins is variable: for asymptomatic liver enzyme elevation, the majority are attributable to the higher dose; in contrast for muscle aches, the majority are not.

Keywords
Adverse events, meta-analysis, side-effects, statins

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Introduction

Patients and doctors need clear reliable information about benefits and risks to make informed decisions. The benefit of statin therapy on death, stroke, and heart attack is quantified against placebo control, but side effect information is not. Adverse events listed for statins come from many sources, most unable to differentiate between events caused by the drug and spontaneous events. Patients reporting symptoms during statin therapy need straightforward information concerning the likelihood that this symptom is truly caused by the drug. For example, the evidence concerning the risk of myopathy and rhabdomyolysis is conflicting.

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Three observational studies[1–3] reported an association with statins, but a later study[4] found no increased risk of severe muscle side effects with statins. The majority of meta-analyses of RCT trial data, however, have supported the relative safety of statins in relation to muscle-related side effects.[5–7] Practising doctors might find it difficult to differentiate between side effects pharmacologically caused by statins and those that are spontaneous or attributable to the nocebo effect: the flip-side of the placebo effect, where patients experience unpleasant effects through negative expectations.[8,9]

The present study compiles the placebo-controlled evidence on adverse events pharmacologically mediated by statins, in a clear form for use with patients. First, we differentiate between adverse events caused by statins and those simply occurring during statin use, through comparison of the two arms of randomized placebo-controlled trials in primary and secondary prevention. Second, we present a clear, understandable metric for everyday clinical use to advise patients whether symptoms being experienced are genuinely pharmacologically caused by the statin: the proportion of symptoms nonpharmacological (PSN).[10]

Methods

Search strategy

We searched MEDLINE/PubMed and the Cochrane Collaboration from inception to December 2012 using keywords and MeSH terms related to statins, placebo, randomized control trials (RCTs), and cardiovascular disease. We also searched bibliographies of systematic reviews.[11–15]

Eligibility criteria

To be eligible for inclusion in this meta-analysis, trials had to: (1) be double-blinded RCTs comparing statins against placebo for cardiovascular prevention; and (2) report information on side effects in statin and placebo arms separately. Studies were excluded if they: (1) were unblinded; (2) focused on patients on renal dialysis[16] or with organ transplants[17–19] because their comorbidities may influence adverse events recorded and make them unrepresentative of the majority of patients; or (3) selectively introduced non-statin medication into either arm.

Data collection and analysis

We recorded adverse events and all-cause mortality, fatal or nonfatal MI and fatal or nonfatal cerebrovascular accident (stroke). Withdrawals and serious adverse events (defined as medical occurrences that either result in death, are life threatening, require hospitalization, or result in intervention) were also recorded.

Meta-analysis was performed using Comprehensive Meta Analysis version 2 (Biostat, New Jersey). We applied a random-effects model due to trial heterogeneity. Total number of patients (the denominator) differed between categories of side effect, as not all studies reported the same categories. We included side effects reported in at least two trials whose total sample size was at least 500. For each side effect, I^2 was calculated to assess heterogeneity. $p < 0.05$ was considered significant.

Second, we calculated the absolute increase in risk for each side effect in the statin arm, where p_{Statin} and p_{Placebo} are the probability in the respective arms: absolute increase in risk $= p_{\text{Statin}} - p_{\text{Placebo}}$. Among patients reporting a side effect, the proportion who would not have had the side effect without the drug was calculated as the absolute increase in risk divided by the rate in the drug arm.

Third, we calculated the PSN[10] for those symptoms that were statistically significant in patients taking statins. The PSN is defined as the proportion of symptoms not attributable to its pharmacological action:

$$\text{Proportion of symptoms nonpharmacological} = \left[1 - \frac{(\rho_{Statin} - \rho_{Placebo})}{\rho_{Statin}}\right] \times 100\%$$

Results

Systematic retrieval of randomized controlled trial data

From 62 full-text articles meeting inclusion criteria (Appendix 1, available online), 20 were excluded for comparing statin with standard therapy or no-treatment, six for not showing side effect data, two for not reporting side effects separately for the arms, and four for focusing on renal dialysis and transplant patients. Several studies performed placebo run-in periods before the main RCT to confirm compliance. The one study with statin run-in which disqualified patients reporting side effects at that stage[20] was excluded because of risk of bias for our symptom meta-analysis. Overall, 14 primary prevention RCTS with 46,262 subjects and 15 secondary prevention RCTs with 37,618 subjects were included in the final analysis (R1–32 Appendix 2). Table 1 shows a summary of these trials.

Table 1. Summary of primary and secondary randomized controlled trials testing statins vs. placebo included in meta-analysis.

Trial	N	Treatment Arm	Average follow-up (years)	Mean age (years)	Male %	Diabetes Mellitus %	Current Smokers %	Mean SBP (mmHg)	% Reduction in LDL-C		% Total Mortality	
									Statin	Placebo	Statin	Placebo
Primary Prevention Randomised Control Trials												
Jupiter[R1]	17802	Rosuvastatin 20	1.9*	66	62	0	16	–	49	−1	2.2	2.8
AFCAPS/TexCAPS[R2,R3]	6605	Lovastatin 20–40	5.2	58	85	2.5	12.4	138	–	–	2.4	2.3
WOSCOPS[R4]	6595	Pravastatin 40	4.9	55	100	1	44	135	26	0	3.2	4.1
PROSPER[R5]	5804	Pravastatin 40	3.2	75	48	11	27	155	34	2	10.3	10.5
CARDS[R6]	2838	Atorvastatin 10	3.9*	62	68	100	22	144	31	−3	4.3	5.8
ASPEN[R7]	2410	Atorvastatin 10	4*	61	66	100	12	133	30	1	5.8	5.7
HYRIM[R8]	568	Fluvastatin 40	4	57	100	–	21	141	22	9	1.4	1.8
CAUIS[R9,R10]	305	Pravastatin 40	3	55	53	–	24	134	22	−2	–	–
KAPS[R11]	447	Pravastatin 40	3	57	100	2.5	26.2	136	29	−4	1.3	1.8
BAK[R12]	215	Pravastatin 40	0.5	55	100	–	25.6	135	–	–	–	–
EXCEL[R13]	977	Lovastatin 20–40	2	57	53	–	–	–	–	–	–	–
Pravastatin Group[R14]	1062	Pravastatin 20	0.5	55	77	–	29	–	26	0	–	–
Cowell et al.[R15]	155	Atorvastatin 80	2*	68	70	4.5	28	144	53	0	3.9	6.4
METEOR[R16]	984	Rosuvastatin 40	2	57	60	0	4	124	49	0	0.0	0.0
Secondary Prevention Randomised Control Trials												
4S[R17]	4444	Simvastatin 20	5.4*	59	81.4	4.5	26	139	35	−1	8.0	12.0
CARE[R18]	4159	Pravastatin 40	5*	59	86	14	21	129	32	4	8.6	9.4
FLARE[R19]	834	Fluvastatin 40 bd	0.8	61	83	4	29	–	34	3	0.7	1.6
LIPID[R20]	9014	Pravastatin 40	6.1	62	83	9	10	–	23	0	11.0	14.1
LIPS[R21]	1677	Fluvastatin 80	3.9*	60	84	12	27	128	27	−11	4.3	5.9
MAAS[R22]	381	Simvastatin 20	4	55	88	0	24	–	–	–	–	–
PLAC I[R23]	408	Pravastatin 40	3	57	77.5	–	17	–	28	−1	1.9	3.0
REGRESS[R24]	884	Pravastatin 40	2	56	100	0	28	135	25	−2	1.1	1.6
SCAT[R25]	460	Simvastatin 10–40	4	61	89	11	15	130	31	−3	5.7	2.6
SPARCL[R26,R27]	4731	Atorvastatin 80	4.9*	63	60	17	19	139	45	4	9.1	8.9
LCAS study[R28]	429	Fluvastatin 20	2.5	59	81	4	20	124	24	4	1.4	2.3
CORONA[R29]	5011	Rosuvastatin 10	2.7*	73	76	29	9	129	44	1	30.0	30.3
Riegger et al.[R30]	365	Rosuvastatin 40–80	1	60	62	5	10	137	27	8	1.1	2.2
GISSI-HF[R31]	4574	Rosuvastatin 10	3.9*	68	77	26	14	127	27	2	29.0	28.0
MARS[R32]	247	Lovastatin 80	2.2	58	91	0	–	125	38	1	1.6	0.8

The average follow-up is that presented in the paper, which is the mean follow-up except where marked * where it is median follow-up; With the drug the daily dose in milligrams is given, bd represents twice a day. Negative values for percentage reduction in LDL-C indicate a percentage increase.

Comparison of adverse events between the statin and placebo arms

Table 2 shows a comparison of the adverse events in the statin and placebo arms in primary prevention RCTs. Table 3 shows this for secondary prevention RCTs. In the 14 primary prevention RCTs, randomization to statin rather than placebo significantly increased the rate of diabetes by 0.5% (95% confidence interval 0.1 to 1%, $p = 0.012$) and significantly reduced deaths by a similar rate, 0.5% (−0.9 to −0.2%, $p = 0.003$).

In the 15 secondary prevention RCTs, randomization to statin rather than placebo significantly reduced deaths by an absolute 1.4% (−2.1 to −0.7%, $p < 0.001$). Only one of these trials reported rates of development of diabetes and it showed no significant effect (95% CI −0.5 to 1.6%, $p = 0.387$).

No other symptom was significantly affected. Importantly, the many side effects commonly attributed to statins (e.g. myopathy, fatigue, muscle aches, rhabdomyolysis, or rise in creatinine kinase >10 upper limit of normal) were no more common in the statin arm than the placebo arm.

In both primary and secondary prevention studies, an asymptomatic rise in liver transaminases was more common when randomized to statin: by 0.4% (0.2 to 0.6%, $p = 0.024$) in primary prevention and by 0.4% (0.2 to 0.7%, $p = 0.006$) in secondary prevention.

Serious adverse effects and withdrawal data

In no study was the rate of serious adverse events significantly greater with statin than placebo. Serious adverse events occurred in nine of 14 primary prevention trials; in 14.6% of patients receiving statins (range 0.9 to 55.6%) and 14.9% of patients receiving placebo (range 0 to 55.1%, $p = 0.83$, $I^2 = 50.4$). Serious adverse events occurred in five of 15 secondary prevention trials; in 9.9% of patients receiving statins (range 0.5 to 65.1%) and 11.2% of patients receiving placebo (range 0.6 to 66.5%, $p = 0.09$, $I^2 = 69.2$).

Withdrawals were reported in 10 of 14 primary prevention trials. In 12.1% of patients receiving statins and 13.4% of patients receiving placebo ($p = 0.03$, $I^2 = 66.3$). Withdrawals were reported in nine of 15 secondary prevention trials; in 12.9% of patients receiving statins and 15.2% of patients receiving placebo ($p = 0.05$, $I^2 = 87.0$; Figure 1).

Proportion of symptoms nonpharmacological

We calculated PSN for symptoms that were statistically significantly increased on statins. In patients with liver transaminases more than three times upper limit of normal, PSN was 76.1% in primary and 77.0% in secondary prevention trials. Similarly, for new diagnosis of diabetes mellitus in primary prevention trials, PSN was 80.2%.

Discussion

In the 83,880 patients receiving blinded placebo-controlled statin therapy, there is little evidence of incremental symptomatic side effects beyond placebo. A patient and doctor wanting to judge the risk–benefit trade off for statin treatment need valid, clear information. For those symptoms statistically significantly increased on statins, we have calculated the PSN, which is easily comprehended by patient and doctor, supporting informed consent.

Side effects genuinely attributable to statin therapy

Diabetes was increased by statins, as has recently been reported.[21–24] Across both primary and secondary prevention trials, the rate of developing diabetes with statin was 3%, against 2.4% with placebo, giving a PSN of 80%. This means that, of all new diabetes diagnoses on statins, 20% (0.6/3.0) were directly pharmacologically attributable to statins. Nevertheless, despite this increase in diabetes, no trial of statins, regardless of length, has ever demonstrated an increase in cardiovascular events.

The only significant adverse event recorded in both primary and secondary prevention was asymptomatic raised liver enzymes. Whether this asymptomatic elevation of liver enzymes by statins is harmful is unclear. In real-world practice outside trials, some patients already have baseline elevation of liver enzymes from comorbidities (e.g. obesity and diabetes mellitus) leading to nonalcoholic fatty liver disease. A recent literature review[25] advocates intentional administration of statins for patients with liver enzymes elevated by stable chronic liver disease.

Comparison with real-life clinical experience

Many real-world patients report muscle-related symptoms with statins. This contrasts with the low placebo subtracted rate in blinded trials shown in this meta-analysis. Several explanations are possible. First, commercial sponsors of clinical trials may not be motivated to search exhaustively for potential side effects. One pointer towards this is that, although liver transaminase elevation was documented in the majority of trials, new diagnosis of diabetes was only documented in three of the 29 trials. Second, many trials do not state clearly how and how often adverse effects were assessed.

Table 2. Analysis of events reported in primary prevention randomized controlled trials.

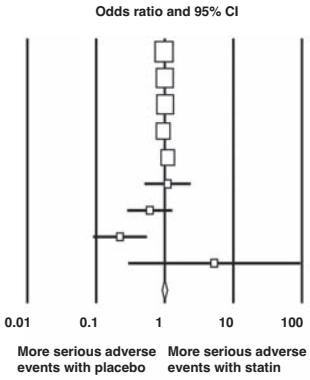
Event described with statin therapy	Number of studies reporting this event	I^2	Statin			Placebo			Absolute risk increase resulting from statins (95% Confidence Intervals)	*p* value	In what proportion of patients with this adverse experience is the statin to blame (%)	Proportion of symptoms Non-pharmacological % (PSN)
			n (SE)	*n* (total)	%	*n* (SE)	*n* (total)	%				
Increased by more than chance												
Liver tranasminases >3ULN	11	0	369	23,518	1.6	265	22,203	1.2	0.4% (0.2% to 0.6%)	0.024	23.9	76.1
Newly diagnosed DM	2	0	281	10,329	2.7	225	10,311	2.2	0.5% (0.1% to 1%)	0.012	19.8	80.2
Indistinguishable from placebo												
Nausea	2	0	36	2,130	1.7	20	1,692	1.2	0.5% (−0.2% to 1.3%)	0.416		
Myopathy symptoms and CK>10 ULN	10	0	16	19,286	0.1	10	17,888	0.1	0% (0% to 0.1%)	0.905		
Renal disorder	2	0	551	9,603	5.7	488	9,183	5.3	0.4% (−0.2% to 1.1%)	0.092		
Insomnia	2	0	231	10,329	2.2	213	10,311	2.1	0.2% (−0.2% to 0.6%)	0.452		
CK >10 ULN and no muscle-related symptoms	7	78	45	17,303	0.3	41	16,885	0.2	0% (−0.1% to 0.1%)	0.100		
Diarrhoea	2	0	59	2,130	2.8	44	1,692	2.6	0.2% (−0.9% to 1.2%)	0.966		
Muscle aches	9	0	1744	22,058	7.9	1646	21,624	7.6	0.3% (−0.2% to 0.8%)	0.407		
Fatigue	2	0	316	10,329	3.1	304	10,311	2.9	0.1% (−0.4% to 0.6%)	0.627		
Gastrointestinal disturbance	4	15	1,765	9,732	18.1	1,722	9,734	17.7	0.4% (−0.6% to 1.5%)	0.429		
Dyspepsia	2	0	59	1,652	3.6	58	1,633	3.6	0% (−1.2% to 1.3%)	0.967		
Newly diagnosed cancer	7	0	735	19,303	3.8	742	19,317	3.8	0% (−0.4% to 0.3%)	0.852		
Rhabdomyolysis	10	0	3	20,046	0.0	3	18,641	0.0	0% (0% to 0%)	0.964		
Constipation	2	0	29	2,130	1.4	28	1,692	1.7	−0.3% (−1.1% to 0.5%)	0.114		
Decreased by more than chance												
Myocardial Infarction	8	29.5	372	18,521	2.0	562	18,481	3.0	−1% (−1.4% to −0.7%)	<0.001		
CVA	8	30.4	136	18,521	0.7	196	18,481	1.1	−0.3% (−0.5% to −0.1%)	0.008		
Death from any cause	10	0	662	21,621	3.1	770	21,503	3.6	−0.5% (−0.9% to −0.2%)	0.003		

Table 3. Analysis of events reported in secondary prevention randomized controlled trials.

Event described with statin therapy	Number of studies reporting this event	I^2	Statin			Placebo			Absolute risk increase resulting from statins (95% Confidence Intervals)	*p* value	In what proportion of patients with this adverse experience is the statin to blame (%)	Proportion of symptoms Non-pharmacological % (PSN)
			n (SE)	*n* (total)	%	*n* (SE)	*n* (total)	%				
Increased by more than chance												
Liver tranasminases >3ULN	13	67	351	18,202	1.9	270	18,174	1.5	0.4% (0.2% to 0.7%)	0.006	23.0	77.0
Indistinguishable from placebo												
Rhabdomyolysis	5	0	3	7,908	0.0	2	7,899	0.0	0% (0% to 0.1%)	0.656		
CK >10 ULN and no muscle-related symptoms	9	23	26	12924	0.2	18	12926	0.1	0.1% (0% to 0.2%)	0.278		
Back pain	2	0	266	2,815	9.4	242	2,800	8.6	0.8% (−0.7% to 2.3%)	0.259		
Muscle aches	6	0	388	8,129	4.8	373	8,152	4.6	0.2% (−0.5% to 0.8%)	0.558		
Headache	3	51	288	3,224	8.9	280	3,225	8.7	0.3% (−1.1% to 1.6%)	0.731		
Newly diagnosed cancer	9	0	835	13,351	6.3	841	13,348	6.3	0% (−0.6% to 0.5%)	0.890		
Gastrointestinal disturbance	4	73	242	5,438	4.5	285	5,439	5.2	−0.8% (−1.6% to 0%)	0.858		
Renal disorder	4	9	29	5,199	0.6	36	5,211	0.7	−0.1% (−0.4% to 0.2%)	0.397		
Suicide	4	0	19	9,444	0.2	26	9,454	0.3	−0.1% (−0.2% to 0.1%)	0.327		
Myopathy symptoms and CK>10 ULN	9	0	9	14,685	0.1	22	14,673	0.1	−0.1% (−0.2% to 0%)	0.343		
Decreased by more than chance												
Myocardial Infarction	11	17.3	897	15,595	5.8	1253	15,598	8.0	−2.3% (−2.8% to −1.7%)	<0.001		
CVA	7	40.4	474	13,802	3.4	572	13,808	4.1	−0.7% (−1.2% to −0.3%)	0.028		
Death	14	56	2545	19,605	13.0	2801	19,475	14.4	−1.4% (−2.1% to −0.7%)	<0.001		

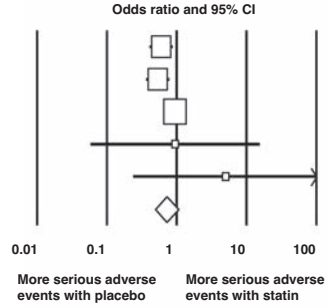
(a) Primary Prevention- Serious adverse events

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Jupiter	0.979	0.902	1.062	−0.520	0.603
AFCAPS/TexCAPS	1.005	0.908	1.113	0.103	0.918
PROSPER	1.023	0.922	1.134	0.427	0.669
CARDS	0.950	0.809	1.115	−0.631	0.528
ASPEN	1.108	0.939	1.308	1.210	0.226
CAUIS	1.103	0.513	2.372	0.251	0.802
KAPS	0.608	0.288	1.284	−1.305	0.192
The Pravastatin Group	0.223	0.091	0.546	−3.284	0.001
METEOR	5.273	0.296	93.909	1.132	0.258
Total	0.990	0.907	1.081	−0.221	0.825



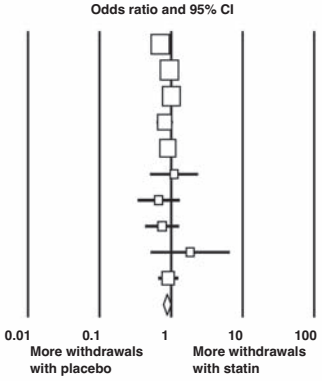
(b) Secondary Prevention- Serious adverse events

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
CARE	0.599	0.411	0.871	−2.678	0.007
REGRESS	0.537	0.367	0.784	−3.213	0.001
CORONA	0.940	0.837	1.057	−1.037	0.300
Riegger et al	0.952	0.059	15.330	−0.035	0.972
GISSI-HF	5.013	0.241	104.478	1.040	0.298
Total	0.720	0.492	1.053	−1.692	0.091



(c) Primary Prevention- Withdrawal from clinical trials

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
AFCAPS/TexCAPS	0.708	0.639	0.785	−6.576	0.000
WOSCOPS	0.944	0.850	1.049	−1.065	0.287
PROSPER	1.008	0.895	1.136	0.136	0.892
CARDS	0.815	0.633	1.049	−1.586	0.113
ASPEN	0.898	0.742	1.087	−1.105	0.269
CAUIS	1.103	0.513	2.372	0.251	0.802
KAPS	0.669	0.343	1.303	−1.182	0.237
The Pravastatin Group	0.749	0.439	1.277	−1.062	0.288
Cowell et al	1.850	0.519	6.595	0.949	0.343
METEOR	0.912	0.665	1.251	−0.570	0.569
Total	0.872	0.770	0.988	−2.152	0.031



(d) Secondary Prevention- Withdrawal from clinical trials

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
4S	0.767	0.638	0.922	−2.828	0.005
CARE	0.392	0.315	0.489	−8.364	0.000
FLARE	1.661	0.954	2.891	1.794	0.073
LIPS	0.668	0.549	0.814	−4.008	0.000
REGRESS	1.563	0.701	3.483	1.093	0.275
CORONA	0.880	0.767	1.009	−1.830	0.067
GISSI-HF 2008	0.927	0.821	1.047	−1.223	0.221
MARS	0.492	0.120	2.012	−0.988	0.323
Riegger et al	0.806	0.497	1.305	−0.877	0.380
Total	0.794	0.630	1.000	−1.959	0.050

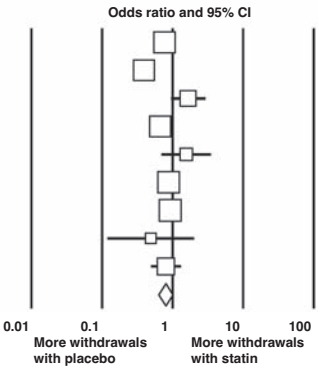


Figure 1. Forest plots illustrating significant adverse events and withdrawal from trials.
Serious adverse events were reported in nine out of 14 primary prevention trials and in five out of 15 secondary prevention trials. Withdrawal from trial was reported in 10 out of 14 primary prevention trials and nine out of 15 secondary prevention trials. In both primary and secondary prevention RCTs, there were higher serious adverse events and withdrawals recorded in the placebo than the statin arm.

Future trials might usefully do this. Third, some trials' inclusion criteria narrow the population spectrum by excluding patients with severe diabetes mellitus, renal failure or hypertension. Fourth, trial volunteers are unavoidably selected for enthusiasm and may therefore be less likely to report side effects than patients in routine clinical practice. They are known to have lower rates of discontinuation of cholesterol lowering therapy.[26,27] Fifth, many trials[R1,R5,R6,R7,R11,R12,R13,R17,R20,R28,R29,R30] (Appendix 2) in our meta-analysis had a placebo run-in period nominally to ensure adequate compliance with medication. This might have enriched the cohort with highly motivated participants. Finally, many trials excluded patients on medication sharing the same hepatic metabolic pathway as statins (e.g. fibrates and macrolide antibiotics). Patients on such drugs might well suffer higher rates of pharmacologically mediated effects.

Comparison of adverse events using different statin intensity regimes

For each adverse event, the balance of pharmacologically and nonpharmacologically mediated effects may be different. Mechanistically, a higher proportion of pharmacological mediation might be expected for some adverse events (e.g. myopathy where previous research has shown muscle toxicity in biopsy specimens of statin treated patients),[28,29] than for other more common adverse events (e.g. fatigue). To further understand this interaction, we reviewed five recent RCTs[30–34] that compared high to low-intensity statin regimes, and performed a meta-analysis of side effects experienced in both arms (Table 4). This analysis showed in the high-intensity, as compared to the low-intensity, statin regimes, statistically significant increases in asymptomatic elevation in liver transaminases and myopathy symptoms with creatinine kinase elevation >10 upper limit of normal and muscle aches and statistically significant reductions in myocardial infarction and cerebrovascular accident. For asymptomatic liver enzyme elevation, the majority (71%) of that experienced by those on the higher dose was attributable to being on the higher dose rather than the lower dose. For muscle aches, however, the majority (84%) was not.

These dose-comparison data suggest that the reason for the relatively high PSN in our meta-analysis might be the low-intensity statin regimes used in most endpoint trials. The FDA's adverse event reporting system has shown an increase in rhabdomyolysis in patients receiving high dose simvastatin and has led the FDA to advise restricting use of simvastatin 80 mg. Nevertheless, the regimes trialled did demonstrate substantial survival advantage.

A patient developing symptoms on a statin: PSN in patient information leaflets

Patients and doctors need information from blinded trials to decide whether to abort therapy if adverse effects occur on statins. Unblinded data, such as those used to construct side effect lists, could be biased upwards by various mechanisms including spontaneous symptoms, nocebo effect,[35] and classical conditioning.

Patient information leaflets inside medication packaging are the first port of call for a patient noticing a new symptom. Currently, they list all symptoms previously reported, with no indication of whether they are more common on drug than placebo.[10] A patient finding their symptom on the list is likely to conclude that it is caused by the medication and may decide to stop it. Even during a later consultation, their physician currently has no ready source of quantitative information to provide. Presenting PSN within the patient information leaflet could give the patient much-needed information at the time of symptom onset, instead of leading them to assume the drug is the cause. During their later consultation, physician and patient reviewing the same PSN information may assist patient decision making.

Limitations

Not all statins, nor all doses, could be addressed by our meta-analysis. The eligible placebo-controlled trials tended to be of relatively low-strength statin regimes. We examined all statins together rather than stratifying them by molecule or dose. This was to enhance the identification of class effects arising at doses supported by evidence of endpoint benefit. However, this approach could underestimate an effect that was more prominent in a subgroup.

A common limitation of meta-analysis is the variation in how outcomes are assessed and reported between the included trials. In these RCTs, withdrawals were sometimes described in total terms, or sometimes categorized by cause (due to 'serious adverse events' or 'drug-related'). For consistency we used total withdrawals in each study.

Conclusion

At the doses tested in these 83,880 patients, only a small minority of symptoms reported on statins are genuinely due to the statins: almost all reported symptoms occurred just as frequently when patients were administered placebo. New-onset diabetes mellitus was the only potentially or actually symptomatic side effect whose rate was significantly higher on statins than placebo; nevertheless, only 1 in 5 of these new cases were actually caused by statins.

Table 4. Analysis of events reported in low-intensity vs. high-intensity statin trials.

Event described with statin therapy	Number of studies reporting this event	I^2	Low intensity statin			High intensity statin			Absolute risk increase resulting from statins (95% Confidence Intervals)	*p* value	In what proportion of patients with this adverse experience is the higher dose statin to blame (%)	Proportion of symptoms not dose related
			n (SE)	*n* (total)	%	*n* (SE)	*n* (total)	%				
Increased by more than chance												
Liver tranasminases >3ULN	5	18.8	59	19783	0.3	205	19829	1.0	−0.7% (−0.9% to −0.6%)	<0.001	71.3	28.7
Myopathy symptoms and CK>10 ULN	5	90.5	59	19783	0.3	139	19829	0.7	−0.4% (−0.5% to −0.3%)	0.012	57.1	42.9
Muscle aches	2	91.4	284	9455	3.0	337	9434	3.6	−0.6% (−1.1% to −0.1%)	0.037	16.0	84.0
Indistinguishable from placebo												
Rhabdomyolysis	5	5.7	6	19783	0.0	13	19829	0.1	0% (−0.1% to 0%)	0.456		
New diagnosis cancer	2	0	341	11039	3.1	332	11026	3.0	0.1% (−0.4% to 0.5%)	0.857		
Death from any cause	5	14.5	1376	19783	7.0	1320	19829	6.7	0.3% (−0.2% to 0.8%)	0.250		
Decreased by more than chance												
MI	5	0	1142	19783	5.8	973	19829	4.9	0.9% (0.4% to 1.3%)	<0.001		
CVA	5	0	667	19783	3.4	570	19829	2.9	0.5% (0.2% to 0.8%)	0.005		

Higher doses of statins produce a detectable effect, but even still the proportion that is attributable to statins varies between the side effects. For asymptomatic liver enzyme elevation, the majority is attributable to the higher statin dose; in contrast for muscle aches, the majority are not.

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Conflict of interest

The authors declare that there is no conflict of interest.

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