Journal Club:
Assessment of adverse effects attributed to statin therapy in product labels: a meta-analysis of double-blind randomised controlled trials

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Assessment of adverse effects attributed to statin therapy in product labels: a meta-analysis of double-blind randomised controlled trials

Cholesterol Treatment Trialists' (CTT) Collaboration †

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Summary

Background Statin product labels (eg, Summaries of Product Characteristics [SmPCs]) list certain adverse outcomes as potential treatment-related effects based mainly on non-randomised and non-blinded studies, which might be subject to bias. We aimed to assess the evidence for such undesirable effects more reliably through a meta-analysis of individual participant data from large double-blind trials of statin therapy.

Methods In this meta-analysis of individual participant-level data from double-blind randomised controlled trials, we generated a list of all undesirable effect terms listed in statin SmPCs by searching an electronic medicines compendium for five statins (atorvastatin, fluvastatin, pravastatin, rosuvastatin, and simvastatin). Randomised trials were eligible for meta-analysis of these effects if they involved at least 1000 participants, had a scheduled treatment period of at least 2 years, and involved a double-blind comparison of statin versus placebo or of a more intensive versus a less intensive statin regimen. Event rate ratios (RRs) and 95% CIs were calculated with statistical significance assessed after controlling the false discovery rate (FDR) at 5%.

Findings 19 trials compared statin versus placebo (123 940 participants, median follow-up 4·5 years [IQR 3·1–5·4]). In addition to previously reported effects on muscle outcomes and diabetes, only four of 66 further undesirable outcomes that had been attributed to statins were FDR significant: abnormal liver transaminases (783 participants [0·30% per annum] allocated statin *vs* 556 [0·22% per annum] allocated placebo, RR 1·41 [95% CI 1·26–1·57]) and other liver function test abnormalities (651 participants [0·25% per annum] allocated statin *vs* 518 [0·20% per annum] allocated placebo, RR 1·26 [1·12–1·41]; absolute annual excess of 0·13% for combined liver function test abnormality), urinary composition alteration (556 [0·21% per annum] allocated statin *vs* 472 [0·18% per annum] allocated placebo, RR 1·18 [1·04–1·33]), and oedema (3495 [1·38% per annum] allocated statin *vs* 3299 [1·31% per annum] allocated placebo, RR 1·07 [1·02–1·12]). Analysis of the four trials of more intensive versus less intensive statin regimens also found significant excesses for abnormal liver transaminases and other liver function test abnormalities (supporting a dose-dependent effect), but no significant excess was found for urinary composition alteration or oedema.

Interpretation Adverse event data from blinded randomised trials do not support causal relationships between statin therapy and most of the conditions (including cognitive impairment, depression, sleep disturbance, and peripheral neuropathy) listed in product labels as potential undesirable effects. In light of these findings, such labelling and other official sources of health information should be revised so that patients and their doctors can make appropriately informed decisions regarding statin therapy.

Implications of all the available evidence

These findings indicate that, in addition to the previously reported adverse effects of statin therapy on muscle outcomes and diabetes, statins are associated only with small absolute increases in abnormal liver biochemistry, and possible adverse effects of unknown clinical relevance on urinary composition and oedema, but not with any other outcomes listed in statin SmPCs. Consequently, the undesirable effect sections of statin product labels might overstate risks and mislead clinicians and patients, and should be revised to better support informed, evidence-based decision making.

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Packager: Parke-Davis Div of Pfizer Inc

Category: HUMAN PRESCRIPTION DRUG LABEL

DEA Schedule: None

Marketing Status: New Drug Application

DRUG LABEL INFORMATION

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LIPITOR- atorvastatin calcium tablet, film coated
Parke-Davis Div of Pfizer Inc

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LIPITOR safely and effectively. See full prescribing information for LIPITOR.

LIPITOR® (atorvastatin calcium) tablets, for oral use
Initial U.S. Approval: 1996

RECENT MAJOR CHANGES

Contraindications, Pregnancy and Lactation (4)	Removed 12/2022
Warnings and Precautions, CNS Toxicity (5.5)	Removed 12/2022

INDICATIONS AND USAGE

LIPITOR is an HMG-CoA reductase inhibitor (statin) indicated (1):

- To reduce the risk of:
  - Myocardial infarction (MI), stroke, revascularization procedures, and angina in adults with multiple risk factors for coronary heart disease (CHD) but without clinically evident CHD.
  - MI and stroke in adults with type 2 diabetes mellitus with multiple risk factors for CHD but without clinically evident CHD.
  - Non-fatal MI, fatal and non-fatal stroke, revascularization procedures, hospitalization for congestive heart failure, and angina in adults with clinically evident CHD.
- As an adjunct to diet to reduce low-density lipoprotein (LDL-C) in:
  - Adults with primary hyperlipidemia.
  - Adults and pediatric patients aged 10 years and older with heterozygous familial hypercholesterolemia (HeFH).
- As an adjunct to other LDL-C-lowering therapies to reduce LDL-C in adults and pediatric patients aged 10 years and older with homozygous familial hypercholesterolemia.
- As an adjunct to diet for the treatment of adults with:
  - Primary dysbetaliproteinemia.
  - Hypertriglyceridemia.

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DOSAGE FORMS AND STRENGTHS

Tablets: 10 mg; 20 mg; 40 mg; 80 mg of atorvastatin (3).

CONTRAINDICATIONS

- Acute liver failure or decompensated cirrhosis (4).
- Hypersensitivity to atorvastatin or any excipient in LIPITOR (4).

WARNINGS AND PRECAUTIONS

- *Myopathy and Rhabdomyolysis:* Risk factors include age 65 years or greater, uncontrolled hypothyroidism, renal impairment, concomitant use with certain other drugs, and higher LIPITOR dosage. Discontinue LIPITOR if markedly elevated CK levels occur or myopathy is diagnosed or suspected. Temporarily discontinue LIPITOR in patients experiencing an acute or serious condition at high risk of developing renal failure secondary to rhabdomyolysis. Inform patients of the risk of myopathy and rhabdomyolysis when starting or increasing LIPITOR dosage. Instruct patients to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever (2.5, 5.1, 7.1, 8.5, 8.6).
- *Immune-Mediated Necrotizing Myopathy (IMNM):* Rare reports of IMNM, an autoimmune myopathy, have been reported with statin use. Discontinue LIPITOR if IMNM is suspected (5.2).
- *Hepatic Dysfunction:* Increases in serum transaminases have occurred, some persistent. Rare reports of fatal and non-fatal hepatic failure have occurred. Consider testing liver enzymes before initiating therapy and as clinically indicated thereafter. If serious hepatic injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs, promptly discontinue LIPITOR (5.3).

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥5%) are nasopharyngitis, arthralgia, diarrhea, pain in extremity, and urinary tract infection (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Viatris at 1-877-446-3679 (1-877-4-INFO-RX) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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5 WARNINGS AND PRECAUTIONS

5.1 Myopathy and Rhabdomyolysis

LIPITOR may cause myopathy (muscle pain, tenderness, or weakness associated with elevated creatine kinase [CK]) and rhabdomyolysis. Acute kidney injury secondary to myoglobinuria and rare fatalities have occurred as a result of rhabdomyolysis in patients treated with statins, including LIPITOR.

Risk Factors for Myopathy

Risk factors for myopathy include age 65 years or greater, uncontrolled hypothyroidism, renal impairment, concomitant use with certain other drugs (including other lipid-lowering therapies), and higher LIPITOR dosage *[see Drug Interactions (7.1) and Use in Specific Populations (8.5, 8.6)]*.

Steps to Prevent or Reduce the Risk of Myopathy and Rhabdomyolysis

LIPITOR exposure may be increased by drug interactions due to inhibition of cytochrome P450 enzyme 3A4 (CYP3A4) and/or transporters (e.g., breast cancer resistant protein [BCRP], organic anion-transporting polypeptide [OATP1B1/OATP1B3] and P-glycoprotein [P-gp]), resulting in an increased risk of myopathy and rhabdomyolysis. Concomitant use of cyclosporine, gemfibrozil, tipranavir plus ritonavir, or glecaprevir plus pibrentasvir with LIPITOR is not recommended. LIPITOR dosage modifications are recommended for patients taking certain anti-viral, azole antifungals, or macrolide antibiotic medications *[see Dosage and Administration (2.5)]*. Cases of myopathy/rhabdomyolysis have been reported with atorvastatin co-administered with lipid modifying doses (>1 gram/day) of niacin, fibrates, colchicine, and ledipasvir plus sofosbuvir. Consider if the benefit of use of these products outweighs the increased risk of myopathy and rhabdomyolysis *[see Drug Interactions (7.1)]*.

Concomitant intake of large quantities, more than 1.2 liters daily, of grapefruit juice is not recommended in patients taking LIPITOR *[see Drug Interactions (7.1)]*.

Discontinue LIPITOR if markedly elevated CK levels occur or if myopathy is either diagnosed or suspected. Muscle symptoms and CK elevations may resolve if LIPITOR is discontinued. Temporarily discontinue LIPITOR in patients experiencing an acute or serious condition at high risk of developing renal failure secondary to rhabdomyolysis (e.g., sepsis; shock; severe hypovolemia; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy).

Inform patients of the risk of myopathy and rhabdomyolysis when starting or increasing the LIPITOR dosage. Instruct patients to promptly report any unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

5.2 Immune-Mediated Necrotizing Myopathy

There have been rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use, including reports of recurrence when the same or a different statin was administered. IMNM is characterized by proximal muscle weakness and elevated serum creatine kinase that persists despite discontinuation of statin treatment; positive anti-HMG CoA reductase antibody; muscle biopsy showing necrotizing myopathy; and improvement with immunosuppressive agents. Additional neuromuscular and serologic testing may be necessary. Treatment with immunosuppressive agents may be required. Discontinue LIPITOR if IMNM is suspected.

5.3 Hepatic Dysfunction

Increases in serum transaminases have been reported with use of LIPITOR *[see Adverse Reactions (6.1)]*. In most cases, these changes appeared soon after initiation, were transient, were not accompanied by symptoms, and resolved or improved on continued therapy or after a brief interruption in therapy. Persistent increases to more than three times the ULN in serum transaminases have occurred in approximately 0.7% of patients receiving LIPITOR in clinical trials. There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including LIPITOR.

Patients who consume substantial quantities of alcohol and/or have a history of liver disease may be at increased risk for hepatic injury *[see Use in Specific Populations (8.7)]*.

Consider liver enzyme testing before LIPITOR initiation and when clinically indicated thereafter. LIPITOR is contraindicated in patients with acute liver failure or decompensated cirrhosis *[see Contraindications (4)]*. If serious hepatic injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs, promptly discontinue LIPITOR.

5.4 Increases in HbA1c and Fasting Serum Glucose Levels

Increases in HbA1c and fasting serum glucose levels have been reported with statins, including LIPITOR. Optimize lifestyle measures, including regular exercise, maintaining a healthy body weight, and making healthy food choices.

5.5 Increased Risk of Hemorrhagic Stroke in Patients on LIPITOR 80 mg with Recent Hemorrhagic Stroke

In a post-hoc analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial where 2365 adult patients, without CHD who had a stroke or TIA within the preceding 6 months, were treated with LIPITOR 80 mg, a higher incidence of hemorrhagic stroke was seen in the LIPITOR 80 mg group compared to placebo (55, 2.3% LIPITOR vs. 33, 1.4% placebo; HR: 1.68, 95% CI: 1.09, 2.59; p=0.0168). The incidence of fatal hemorrhagic stroke was similar across treatment groups (17 vs. 18 for the atorvastatin and placebo groups, respectively). The incidence of non-fatal hemorrhagic stroke was significantly higher in the LIPITOR group (38, 1.6%) as compared to the placebo group (16, 0.7%). Some baseline characteristics, including hemorrhagic and lacunar stroke on study entry, were associated with a higher incidence of hemorrhagic stroke in the LIPITOR group *[see Adverse Reactions (6.1)]*. Consider the risk/benefit of use of LIPITOR 80 mg in patients with recent hemorrhagic stroke.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In the LIPITOR placebo-controlled clinical trial database of 16,066 patients (8755 LIPITOR vs. 7311 placebo; age range 10-93 years, 39% women, 91% White, 3% Black, 2% Asian, 4% other) with a median treatment duration of 53 weeks, the most common adverse reactions in patients treated with LIPITOR that led to treatment discontinuation and occurred at a rate greater than placebo were: myalgia (0.7%), diarrhea (0.5%), nausea (0.4%), alanine aminotransferase increase (0.4%), and hepatic enzyme increase (0.4%).

Table 1 summarizes adverse reactions reported in ≥ 2% and at a rate greater than placebo in patients treated with LIPITOR (n=8755), from seventeen placebo-controlled trials.

Table 1: Adverse Reactions Occurring in ≥ 2% in Patients LIPITOR-Treated with any Dose and Greater than Placebo

Adverse Reaction	% Placebo N=7311	% 10 mg N=3908	% 20 mg N=188	% 40 mg N=604	% 80 mg N=4055	% Any dose N=8755
Nasopharyngitis	8.2	12.9	5.3	7.0	4.2	8.3
Arthralgia	6.5	8.9	11.7	10.6	4.3	6.9
Diarrhea	6.3	7.3	6.4	14.1	5.2	6.8
Pain in extremity	5.9	8.5	3.7	9.3	3.1	6.0
Urinary tract infection	5.6	6.9	6.4	8.0	4.1	5.7
Dyspepsia	4.3	5.9	3.2	6.0	3.3	4.7
Nausea	3.5	3.7	3.7	7.1	3.8	4.0
Musculoskeletal pain	3.6	5.2	3.2	5.1	2.3	3.8
Muscle spasms	3.0	4.6	4.8	5.1	2.4	3.6
Myalgia	3.1	3.6	5.9	8.4	2.7	3.5
Insomnia	2.9	2.8	1.1	5.3	2.8	3.0
Pharyngolaryngeal pain	2.1	3.9	1.6	2.8	0.7	2.3

Other adverse reactions reported in placebo-controlled trials include:

Body as a whole: malaise, pyrexia

Digestive system: abdominal discomfort, eructation, flatulence, hepatitis, cholestasis

Musculoskeletal system: musculoskeletal pain, muscle fatigue, neck pain, joint swelling

Metabolic and nutritional system: transaminases increase, liver function test abnormal, blood alkaline phosphatase increase, creatine phosphokinase increase, hyperglycemia

Nervous system: nightmare

Respiratory system: epistaxis

Skin and appendages: urticaria

Special senses: vision blurred, tinnitus

Urogenital system: white blood cells urine positive

Elevations in Liver Enzyme Tests

Persistent elevations in serum transaminases, defined as more than 3 times the ULN and occurring on 2 or more occasions, occurred in 0.7% of patients who received LIPITOR in clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40, and 80 mg, respectively.

One patient in clinical trials developed jaundice. Increases in liver enzyme tests in other patients were not associated with jaundice or other clinical signs or symptoms. Upon dose reduction, drug interruption, or discontinuation, transaminase levels returned to or near pretreatment levels without sequelae. Eighteen of 30 patients with persistent liver enzyme elevations continued treatment with a reduced dose of LIPITOR.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of LIPITOR. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal disorders: pancreatitis

General disorders: fatigue

Hepatobiliary Disorders: fatal and non-fatal hepatic failure

Immune system disorders: anaphylaxis

Injury: tendon rupture

Musculoskeletal and connective tissue disorders: rhabdomyolysis, myositis.

There have been rare reports of immune-mediated necrotizing myopathy associated with statin use.

Nervous system disorders: dizziness, peripheral neuropathy.

There have been rare reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with the use of all statins. Cognitive impairment was generally nonserious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

Psychiatric disorders: depression

Respiratory disorders: interstitial lung disease

Skin and subcutaneous tissue disorders: angioneurotic edema, bullous rashes (including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis)

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	Year of publication of primary results	Number of included participants*	Treatment regimen (mg/day)†	Follow-up (years)	LDL-C (mmol/L)	Age (years)	Women	Men	White participants‡	History of vascular disease	Medical history of diabetes	Timing of scheduled routine follow-up visits	Type of data principally collected
Statin vs placebo													
4S[30]	1994	4444	S20-40 vs placebo	5·4 (5·3–5·6)	4·9 (0·7)	59 (7)	827 (19%)	3617 (81%)	NA	4444 (100%)	202 (5%)	Every 1·5 months until 18 months, then every 6–48 months	All AEs
WOSCOPS[31]	1995	6595	P40 vs placebo	4·8 (4·3–5·3)	5·0 (0·5)	55 (6)	0	6595 (100%)	NA	1066 (16%)	77 (1%)	Every 3 months until final follow-up	All AEs
CARE[32]	1996	4159	P40 vs placebo	4·9 (4·4–5·5)	3·6 (0·4)	59 (9)	576 (14%)	3583 (86%)	3851 (93%)	4159 (100%)	586 (14%)	At 1·5 months, then every 3 months until 72 months	All AEs
AFCAPS/ TexCAPS[33]	1998	6605	L20-40 vs placebo	5·0 (4·7–5·8)	3·9 (0·4)	58 (7)	997 (15%)	5608 (85%)	5860 (89%)	0	155 (2%)	Every 1·5 months until 12 months, 15 months, 18 months then every 6 months until 60 months	All AEs
LIPID[34]	1998	9014	P40 vs placebo	5·9 (5·4–6·4)	3·9 (0·8)	61 (8)	1516 (17%)	7498 (83%)	NA	9014 (100%)	782 (9%)	At 3, 6, 9, 12 months, then annually until 72 months	SAEs
LIPS[35]	2002	1677	F80 vs placebo	4·0 (3·6–4·0)	3·4 (0·8)	60 (10)	271 (16%)	1406 (84%)	1650 (98%)	1677 (100%)	202 (12%)	At 1·5 and 6 months, then every ~6 months	All AEs
HPS[36]	2002	20536	S40 vs placebo	5·2 (4·6–5·6)	3·4 (0·8)	64 (8)	5082 (25%)	15454 (75%)	19901 (97%)	17386 (85%)	5963 (29%)	At 4, 8, and 12 months, then every 6 months until 60 months	SAEs + selected AEs
PROSPER[37]	2002	5804	P40 vs placebo	3·3 (3·0–3·5)	3·8 (0·8)	75 (3)	3000 (52%)	2804 (48%)	NA	2565 (44%)	623 (11%)	Every 3 months until final follow-up	All AEs
ASCOT-LLA[38]	2003	10240	A10 vs placebo	3·3 (2·8–3·7)	3·4 (0·7)	63 (9)	1919 (19%)	8321 (81%)	9687 (95%)	1684 (16%)	2540 (25%)	At 1·5, 3, and 6 months, then every 6 months until 66 months or final follow-up	All AEs
ALERT[39]	2003	2102	F40-80 vs placebo	5·5 (5·2–5·6)	4·1 (1·0)	50 (11)	715 (34%)	1387 (66%)	2039 (97%)	409 (19%)	396 (19%)	At 1·5 months then every 6 months until 72 months	All AEs
CARDS[40]	2004	2838	A10 vs placebo	4·2 (3·4–4·9)	2·9 (0·8)	61 (8)	909 (32%)	1929 (68%)	2676 (94%)	106 (4%)	2838 (100%)	At 1, 2, 3, and 6 months, then every 6 months until 48 months	All AEs
4D[41]	2005	1255	A20 vs placebo	2·7 (1·7–4·0)	3·3 (0·8)	66 (8)	578 (46%)	677 (54%)	924 (74%)	1041 (83%)	1255 (100%)	At 1 and 6 months, then every 6 months until 48 months	All AEs
ASPEN[42]	2006	2410	A10 vs placebo	4·0 (2·9–4·5)	2·9 (0·7)	60 (8)	811 (34%)	1599 (66%)	2029 (84%)	747 (31%)	2410 (100%)	At 1, 2, 3, and 6 months, then every 6 months until 48 months	All AEs
SPARCL[43]	2006	4731	A80 vs placebo	4·9 (4·4–5·5)	3·5 (0·6)	63 (11)	1908 (40%)	2823 (60%)	4415 (93%)	4731 (100%)	794 (17%)	At 1, 3 and 6 months, then every 6 months until 78 months	All AEs
CORONA[44]	2007	4982	R10 vs placebo	2·7 (2·2–3·1)	3·6 (0·9)	72 (7)	1175 (24%)	3807 (76%)	NA	4982 (100%)	1473 (30%)	At 1·5 and 3 months, then every 3 months until 51 months or final follow-up	All AEs
GISSI-HF[45]	2008	4574	R10 vs placebo	3·9 (3·0–4·4)	3·1 (0·9)	68 (11)	1032 (23%)	3542 (77%)	4574 (100%)	4574 (100%)	1196 (26%)	At 1, 3, and 6 months, then every 6 months until 60 months	SAEs + selected AEs
JUPITER[46]	2008	16714	R20 vs placebo	1·9 (1·5–2·4)	2·7 (0·5)	65 (8)	6374 (38%)	10340 (62%)	NA	0	44 (<1%)	At 3 and 6 months, then every 6 months until 36 months, close out	All AEs
AURORA[47]	2009	2555	R10 vs placebo	3·9 (2·2–4·6)	2·6 (0·9)	64 (9)	969 (38%)	1586 (62%)	NA	1025 (40%)	658 (26%)	At 3 and 6 months, then every 6 months until 42 months	All AEs
HOPE-3[48]	2016	12705	R10 vs placebo	5·5 (5·1–6·2)	3·3 (0·9)	66 (6)	5874 (46%)	6831 (54%)	2546 (20%)	0	731 (6%)	At 1·5 and 6 months, then every 6 months until 96 months	SAEs + selected AEs
Subtotal (n=19 studies)	..	123940	..	4·5 (3·1–5·4)	3·5 (0·9)	63 (9)	34533 (28%)	89407 (72%)	60152 (81%)	59610 (48%)	22925 (18%)	..	..

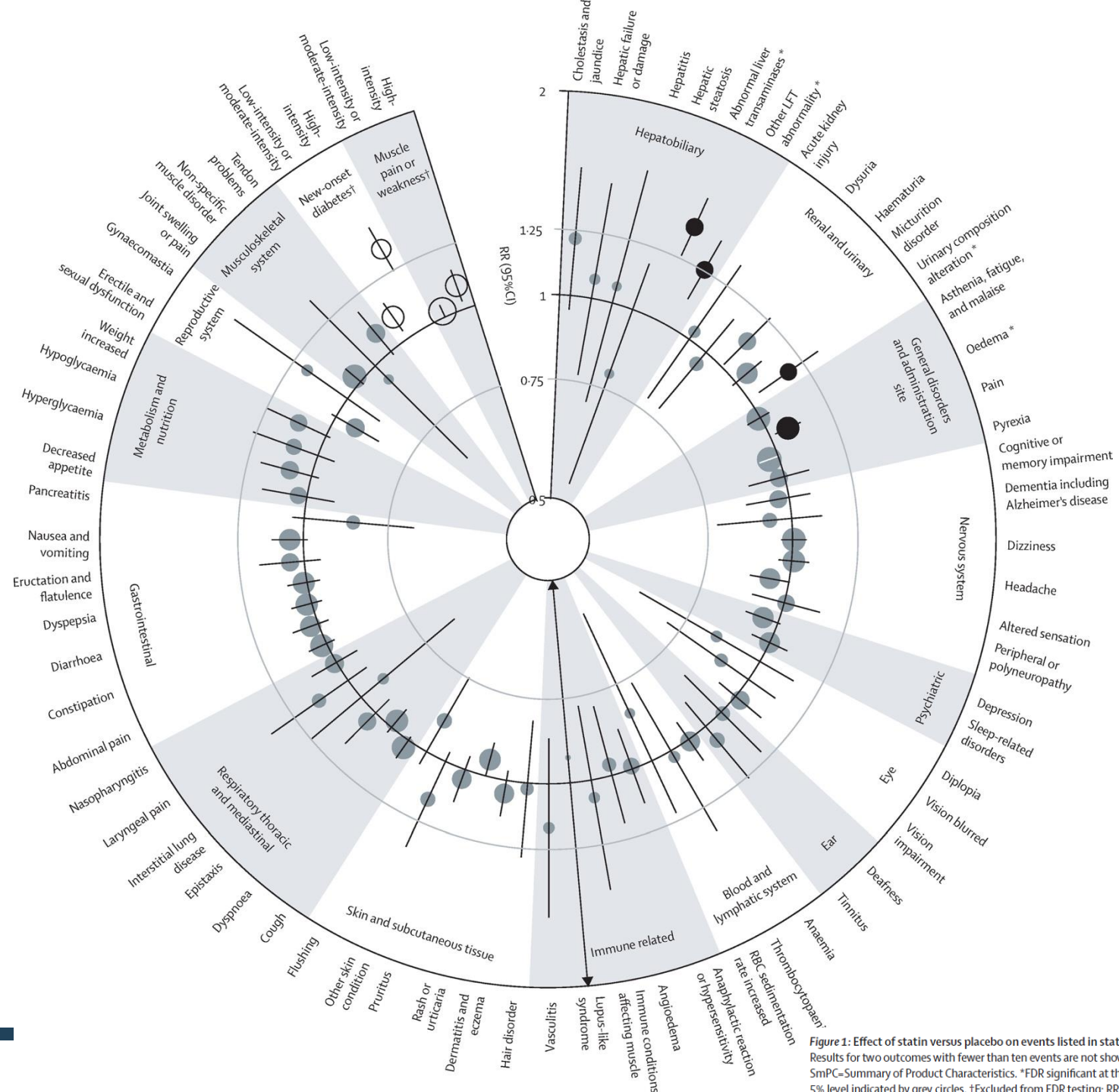
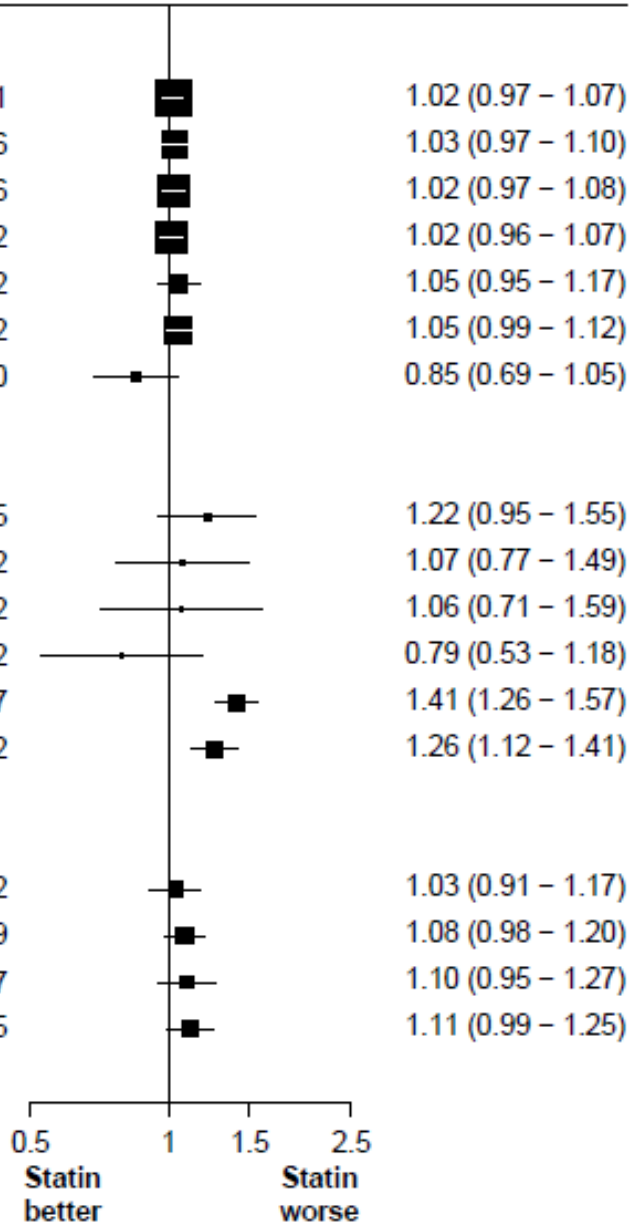


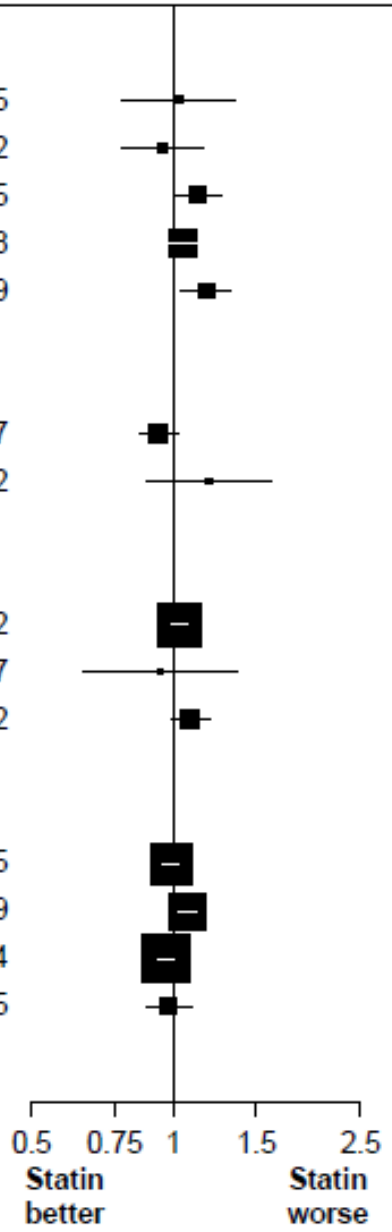
Figure 1: **Effect of statin versus placebo on events listed in statin SmPCs, subdivided by component parts**

Results for two outcomes with fewer than ten events are not shown in the figure, but are included in the appendix. FDR=false discovery rate. LFT=liver function test. RBC=red blood cell. RR=rate ratio. SmPC=Summary of Product Characteristics. *FDR significant at the 5% level; RR for results FDR-significant at the 5% level are indicated by black circles and RR for results not FDR-significant at the 5% level indicated by grey circles. †Excluded from FDR testing; RR for results excluded from FDR testing indicated by white circles.

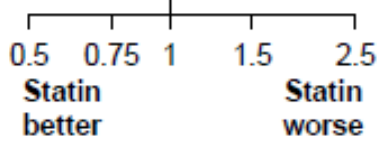
Endpoint	Events (% per annum)		Observed–Expected		Rate Ratio (95% CI)
	Statin (n=62028)	Placebo (n=61912)	O–E	Var(O–E)	
Gastrointestinal disorders					
Abdominal pain	3443 (1.4)	3367 (1.3)	35.4	1702.1	1.02 (0.97 – 1.07)
Constipation	1865 (0.7)	1810 (0.7)	28.3	918.6	1.03 (0.97 – 1.10)
Diarrhoea	2707 (1.1)	2649 (1.0)	28.3	1338.6	1.02 (0.97 – 1.08)
Dyspepsia	2472 (1.0)	2430 (1.0)	18.5	1225.2	1.02 (0.96 – 1.07)
Eructation and flatulence	722 (0.3)	683 (0.3)	18.3	351.2	1.05 (0.95 – 1.17)
Nausea and vomiting	2111 (0.8)	1999 (0.8)	51.3	1027.2	1.05 (0.99 – 1.12)
Pancreatitis	164 (<0.1)	192 (<0.1)	−14.5	89.0	0.85 (0.69 – 1.05)
Hepatobiliary disorders					
Cholestasis and jaundice	144 (<0.1)	118 (<0.1)	12.8	65.5	1.22 (0.95 – 1.55)
Hepatic failure or damage	73 (<0.1)	68 (<0.1)	2.4	35.2	1.07 (0.77 – 1.49)
Hepatitis	48 (<0.1)	45 (<0.1)	1.4	23.2	1.06 (0.71 – 1.59)
Hepatic steatosis	43 (<0.1)	54 (<0.1)	−5.6	24.2	0.79 (0.53 – 1.18)
Abnormal liver transaminases *	783 (0.3)	556 (0.2)	114.2	334.7	1.41 (1.26 – 1.57)
Other LFT abnormality *†	651 (0.3)	518 (0.2)	66.6	292.2	1.26 (1.12 – 1.41)
Metabolism and nutrition disorders **					
Decreased appetite	503 (0.2)	486 (0.2)	8.4	247.2	1.03 (0.91 – 1.17)
Hyperglycaemia	766 (0.3)	706 (0.3)	29.7	367.9	1.08 (0.98 – 1.20)
Hypoglycaemia	373 (0.1)	338 (0.1)	16.3	177.7	1.10 (0.95 – 1.27)
Weight increased	578 (0.2)	516 (0.2)	29.5	273.5	1.11 (0.99 – 1.25)



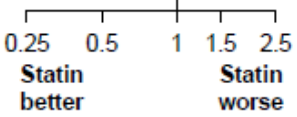
Endpoint	Events (% per annum) Statin (n=62028)	Events (% per annum) Placebo (n=61912)	Observed−Expected O−E	Observed−Expected Var(O−E)	Rate Ratio (95% CI)
Renal and urinary disorders					
Acute kidney injury	103 (<0.1)	99 (<0.1)	1.6	50.5	1.03 (0.78 – 1.36)
Dysuria	192 (<0.1)	201 (<0.1)	−5.0	98.2	0.95 (0.78 – 1.16)
Haematuria	656 (0.3)	578 (0.2)	37.8	308.5	1.13 (1.01 – 1.26)
Micturition disorder	1906 (0.7)	1814 (0.7)	45.0	929.8	1.05 (0.98 – 1.12)
Urinary composition alteration *	556 (0.2)	472 (0.2)	41.9	256.9	1.18 (1.04 – 1.33)
Reproductive system and breast disorders					
Erectile and sexual dysfunction	869 (0.3)	926 (0.4)	−31.9	448.7	0.93 (0.85 – 1.02)
Gynaecomastia	92 (<0.1)	77 (<0.1)	7.3	42.2	1.19 (0.88 – 1.61)
Musculoskeletal and connective tissue disorders					
Joint swelling or pain	4774 (1.9)	4626 (1.9)	73.5	2349.2	1.03 (0.99 – 1.07)
Non−specific muscle disorder	52 (<0.1)	55 (<0.1)	−1.6	26.7	0.94 (0.64 – 1.37)
Tendon problems	899 (0.3)	822 (0.3)	36.2	430.2	1.09 (0.99 – 1.20)
General disorders and administration site conditions					
Asthenia, fatigue and malaise	4253 (1.7)	4281 (1.7)	−19.5	2132.5	0.99 (0.95 – 1.03)
Oedema *	3495 (1.4)	3299 (1.3)	110.8	1695.9	1.07 (1.02 – 1.12)
Pain	5995 (2.4)	6175 (2.5)	−103.4	3041.4	0.97 (0.93 – 1.00)
Pyrexia	675 (0.3)	687 (0.3)	−7.4	340.5	0.98 (0.88 – 1.09)



Endpoint	Events (% per annum)		Observed−Expected		Rate Ratio (95% CI)
	Statin (n=62028)	Placebo (n=61912)	O−E	Var(O−E)	
Nervous system disorders					
Cognitive or memory impairment	616 (0.2)	639 (0.2)	−12.3	313.7	0.96 (0.86 − 1.07)
Dementia including Alzheimer's	231 (<0.1)	249 (<0.1)	−9.3	120.0	0.93 (0.77 − 1.11)
Dizziness	4156 (1.6)	4140 (1.7)	3.3	2073.5	1.00 (0.96 − 1.05)
Headache	2808 (1.1)	2790 (1.1)	6.7	1398.9	1.00 (0.95 − 1.06)
Altered sensation	1573 (0.6)	1673 (0.7)	−55.5	811.4	0.93 (0.87 − 1.00)
Peripheral or poly−neuropathy	543 (0.2)	537 (0.2)	0.9	269.9	1.00 (0.89 − 1.13)
Psychiatric disorders					
Depression	1910 (0.7)	2016 (0.8)	−55.5	981.3	0.95 (0.89 − 1.01)
Sleep−related disorders	1728 (0.7)	1731 (0.7)	−3.1	864.6	1.00 (0.93 − 1.07)
Eye disorders					
Diplopia	77 (<0.1)	91 (<0.1)	−7.3	42.0	0.84 (0.62 − 1.14)
Vision blurred	144 (<0.1)	161 (<0.1)	−8.9	76.2	0.89 (0.71 − 1.11)
Vision impairment	895 (0.3)	881 (0.3)	7.8	443.9	1.02 (0.93 − 1.12)
Ear and labyrinth disorders					
Deafness	228 (<0.1)	225 (<0.1)	0.5	113.2	1.00 (0.84 − 1.21)
Tinnitus	279 (0.1)	262 (0.1)	7.9	135.2	1.06 (0.90 − 1.25)



Endpoint	Events (% per annum)		Observed−Expected		Rate Ratio (95% CI)
	Statin (n=62028)	Placebo (n=61912)	O−E	Var(O−E)	
Blood and lymphatic system disorders					
Anaemia	1236 (0.5)	1228 (0.5)	3.6	615.9	1.01 (0.93 – 1.09)
Eosinophilia	0 (0.0)	1 (<0.1)	−0.5	0.2	
Thrombocytopaenia	92 (<0.1)	90 (<0.1)	1.0	45.5	1.02 (0.76 – 1.37)
RBC sedimentation rate increased †	50 (<0.1)	60 (<0.1)	−5.0	27.5	0.84 (0.57 – 1.21)
Immune related disorders					
Anaphylactic reaction or hypersensitivity	427 (0.2)	431 (0.2)	−2.7	214.5	0.99 (0.86 – 1.13)
Angioedema	179 (<0.1)	185 (<0.1)	−3.6	91.0	0.96 (0.78 – 1.18)
Immune conditions affecting muscle	79 (<0.1)	74 (<0.1)	2.3	38.2	1.06 (0.77 – 1.46)
Lupus−like syndrome	11 (<0.1)	12 (<0.1)	−0.5	5.7	0.92 (0.40 – 2.07)
Serious skin drug reactions	3 (<0.1)	2 (<0.1)	0.5	1.2	1.48 (0.26 – 8.56)
Vasculitis	89 (<0.1)	77 (<0.1)	6.1	41.5	1.16 (0.86 – 1.57)
Skin and subcutaneous tissue disorders					
Hair disorder	143 (<0.1)	140 (<0.1)	1.3	70.7	1.02 (0.81 – 1.29)
Dermatitis and eczema	1278 (0.5)	1223 (0.5)	28.1	625.2	1.05 (0.97 – 1.13)
Rash or urticaria	2147 (0.8)	2259 (0.9)	−63.3	1101.3	0.94 (0.89 – 1.00)
Pruritus	1152 (0.4)	1111 (0.4)	19.6	565.7	1.04 (0.95 – 1.12)
Other skin condition	263 (0.1)	228 (<0.1)	17.5	122.7	1.15 (0.97 – 1.38)
Flushing	252 (<0.1)	283 (0.1)	−16.1	133.7	0.89 (0.75 – 1.05)
Respiratory, thoracic and mediastinal disorders					
Cough	4009 (1.6)	3895 (1.5)	61.3	1975.4	1.03 (0.99 – 1.08)
Dyspnoea	2946 (1.2)	3016 (1.2)	−40.6	1490.1	0.97 (0.92 – 1.02)
Epistaxis	698 (0.3)	667 (0.3)	14.4	341.2	1.04 (0.94 – 1.16)
Interstitial lung disease	73 (<0.1)	80 (<0.1)	−3.7	38.2	0.91 (0.66 – 1.25)
Laryngeal pain	210 (<0.1)	184 (<0.1)	12.1	98.5	1.13 (0.93 – 1.38)
Nasopharyngitis	973 (0.4)	960 (0.4)	5.1	483.1	1.01 (0.92 – 1.10)



Utilization of statins in real-world data

Report category: Data Source Release | Source: OPTUM Extended DOD | Release: 2025-11-04 | Report: Drug Eras

DOMAIN TABLE

DRUG ERA

statin

COLUMNS TO DISPLAY

Concept Id	Concept Name	# People	% People	Records per Person	Median Era Length (Days)
1545958	atorvastatin	9,630,503	9.14 %	2.3	172
1539403	simvastatin	4,725,087	4.49 %	2.5	156
922570	nystatin	4,097,452	3.89 %	1.6	14
1510813	rosuvastatin	3,847,531	3.65 %	2.1	161
1551860	pravastatin	2,293,064	2.18 %	2.2	166

Questions

- How should statistical significance impact the interpretation of safety outcomes?
- How much evidence is necessary to rule out effect?
- How should we distinguish between population-level average treatment effects vs. patient-level risks?
- How should real-world evidence complement what has been learned across randomized trials to inform safety profile?