

### Evidence Tables

#### Are statins effective in improving lipid profiles and other outcomes compared to other treatments or placebo in people with type 2 diabetes?

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding
Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ et al. Rapid emergence of effect of atorvastatin on cardiovascular outcomes in the Collaborative Atorvastatin Diabetes Study (CARDS). Diabetologia 2005; 48(12):2482-2485. Ref ID: 96	Post hoc analysis of CARDS  RCT double blind multicentre 1++	N=2,838 in 132 centres in the UK and Ireland	Inclusion criteria: Men and women aged 40–75 years with T2D diagnosed at least 6 months before study entry were considered for inclusion provided they had at least one or more of the following: a history of hypertension <sup>1</sup> ; retinopathy; microalbuminuria or macroalbuminuria <sup>2</sup> , or currently smoking <sup>3</sup>  Exclusion criteria: Patients were ineligible if they had any past history of MI, angina, coronary vascular surgery, cerebrovascular accident, or severe peripheral vascular disease (defined as warranting surgery).  Patients were asked to attend four pretreatment	Atorvastatin 10mg	Placebo	3.9 years (median follow-up)	<u>Primary endpoint</u> : first of the following: acute coronary heart disease event (MI including silent infarction, unstable angina, acute coronary heart disease death, resuscitated cardiac arrest), coronary revascularisation procedures, or stroke.  <u>Prespecified secondary efficacy outcomes</u> were effect of treatment on total mortality and effect of	As reported in the original CARDS study, at the completion of the trial there was a 37% reduction in the primary endpoint of major CVD events. (There was a reduction of 36% in acute coronary events, 31% in coronary revascularisation events, and 48% in stroke, when assessed separately)  → by 1 year of follow-up the estimate of the treatment effect on the primary endpoint was already at its final values of a 37% reduction and by 18 months the CI did not include unity.	UK Department of Health, Diabetes UK, and Pfizer

<sup>1</sup> defined as receiving antihypertensive treatment or having systolic blood pressure of 140 mm Hg or greater or diastolic blood pressure of 90 mm Hg or greater on at least two successive occasions.

<sup>2</sup> defined as a positive Micral or other strip test, an albumin creatinine ratio of 2.5 mg/mmol or greater, or an albumin excretion rate on timed collection of 20 ug/min or more, all on at least two successive occasions

<sup>3</sup> (no minimum number of cigarettes per day was required). All patients reporting current smoking were counselled to quit.

			visits over a 10-week period. After a 12 h fast. Mean LDL [ ] during baseline visits had to be 4.14 mmol/L or lower and serum triglycerides 6.78 mmol/L or less.  Patients were also excluded if they had a plasma creatinine concentration greater than 150 µmol/L, HbA1c >12% or if during the baseline phase they had less than 80% compliance with placebo.				atorvastatin on any acute, hospital-verified cardiovascular endpoint.  <u>Safety issues</u>		
Shepherd J, Barter P, Carmena R, Deedwania P, Fruchart JC, Haffner S et al. Effect of lowering LDL cholesterol substantially below currently recommended levels in patients with coronary heart disease and diabetes: the Treating to New Targets (TNT) study. Diabetes Care 2006; 29(6):1220-1226. Ref ID: 3399	RCT double blind, multicentre  1++	N= 1,501	Inclusion criteria: men and women aged 35–75 years with clinically evident CHD, defined as previous MI, previous or present angina with objective evidence of atherosclerotic CHD, or previous coronary revascularization procedure. Patients were included in the current analysis if they had prior history of diabetes noted on their pre-screening form (fasting glucose levels at screening were not	Atorvastatin 10mg/day <sup>4</sup> (N= 753)	Atorvastatin 80mg/day (N= 748)	4.9 years (median follow-up)	<u>Primary efficacy outcome:</u> time to first major CV event (death from CHD, nonfatal non-procedure-related MI, resuscitated cardiac arrest, or fatal or nonfatal stroke)  <u>Secondary efficacy outcomes</u>	* Primary efficacy outcomes Over the 5 years of double-blind treatment, a primary event was experienced by 103 patients with diabetes (13.8%) receiving atorvastatin 80 mg and 135 patients (17.9%) receiving atorvastatin 10mg. This represented a 25% reduction in the risk of major cardiovascular events in favour of the high-dose group (HR 0.75 [95% CI 0.58 to 0.97], p>0.026)  A decreased incidence of primary event rates was observed in the atorvastatin 80 compared with the 10-mg group across all quintiles of patient age and duration of diabetes	Pfizer

<sup>4</sup> Any previously prescribed lipid regulating drugs were discontinued at screening, and all patients required a wash-out period of 1–8 weeks (8 weeks for those who had and 1 week for those who had not previously received lipid regulating drugs). To ensure that all patients at baseline achieved LDL cholesterol levels consistent with the current guidelines for the treatment of stable CHD, patients with LDL cholesterol between 130 and 250 mg/dl (3.4 – 6.5 mmol/l) and triglycerides ≤ 600 mg/dl (6.8 mmol/l) entered an 8-week open-label period with atorvastatin 10 mg/day. At the end of the run-in phase (week 0), those patients with a mean LDL cholesterol < 130 mg/dl (3.4 mmol/l) (determined at weeks -4 and -2) were randomized to double-blind therapy with either atorvastatin 10 or 80 mg/day.

		<p>used).</p> <p>Exclusion criteria: Major exclusion criteria included statin hypersensitivity, current liver disease, nephrosis, pregnancy or uncontrolled CHD risk factors, CHD event or revascularization within less than a month, CHF, unexplained creatine phosphokinase levels more than six times the upper limit of normal, life-threatening malignancy, or immunosuppressive or lipid-lowering drug treatment.</p> <p>Baseline characteristics of patients with diabetes were similar between the two treatment groups, as were baseline LDL, TC, Tg and HDL.</p> <p>The proportion of patients managing their diabetes with oral hypoglycaemic agents, insulin, or a combination thereof</p>				<p>included any CV event, major coronary event (CHD death, nonfatal non-procedure-related MI, or resuscitated cardiac arrest), any coronary event, cerebrovascular event, PAD, documented angina, hospitalization for CHF, and all-cause mortality.</p> <p><u>Lipid profile</u></p> <p><u>Safety profile</u></p>	<p>and in patients with HbA1c <math>\leq 7\%</math> and A1C <math>&gt;7\%</math><sup>5</sup></p> <p>* Secondary efficacy outcomes Significant differences between the groups in favour of atorvastatin 80 mg were observed for the secondary outcomes of time to cerebrovascular event (0.69 [0.48 to 0.98], <math>p &lt; 0.037</math>) and time to cardiovascular event (0.85 [0.73 to 1.00], <math>p &lt; 0.044</math>). Consistent with the overall population, there was no significant difference between the treatments for all cause mortality.</p> <p>* Lipid profile LDL End-of-treatment LDL cholesterol levels increased by 3% to a mean of 98.6 mg/dl (2.5 mmol/l) in patients with diabetes who continued atorvastatin 10 mg, while a further reduction of 19% to a mean of 77.0 mg/dl (2.0 mmol/l) was observed in patients with diabetes who were assigned to atorvastatin 80 mg (<math>p &lt; 0.0001</math>).</p> <p>Total Cholesterol At the end of treatment, TC increased from baseline by 2% to a mean of 177.9 mg/dl (4.6 mmol/l) with atorvastatin 10 mg and was further reduced by 13% to a mean of 150.6 mg/dl (3.9 mmol/l) with atorvastatin 80 mg (<math>p &lt; 0.0001</math>).</p>
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<sup>5</sup> Additional benefit from atorvastatin 80 vs. 10 mg was observed early in the disease process of diabetes, with patients across all quintiles of diabetes duration in the atorvastatin 80-mg group experiencing a reduced incidence of first stroke compared with those in the atorvastatin 10-mg group. Moreover, patients with and without good glycemic control randomized to atorvastatin 80 mg experienced a lower incidence of first major cardiovascular event, coronary event, stroke, nonfatal non-procedure-related myocardial infarction, and CHD death than patients randomized to atorvastatin 10 mg, with a significant reduction in risk for major cardiovascular events in patients with A1C  $\leq 7\%$ .

			was similar between treatment groups					<p>Triglycerides Triglycerides increased from baseline by 11% to 178.3 mg/dl (2.0 mmol/l) with atorvastatin 10 mg, while atorvastatin 80mg resulted in an additional reduction of 10% to 145.3 mg/dl (1.6 mmol/l). (p &lt;0.0001)</p> <p>HDL There was little change in HDL cholesterol in either treatment group over the course of the study.</p> <p>*Safety issues Safety and tolerability In the diabetic population, treatment related adverse events were experienced by 41 patients (5.4%) receiving atorvastatin 10 mg and 52 patients (7.0%) receiving atorvastatin 80 mg. These rates are similar to those observed in the overall TNT population (5.8% for atorvastatin 10 mg and 8.1% for atorvastatin 80 mg).</p> <p>Treatment-related myalgia was reported in 27 patients (3.6%) receiving atorvastatin 10 mg and 18 patients (2.4%) receiving atorvastatin 80 mg.</p> <p>Persistent elevations more than three times the upper limit of normal (occurring twice within 4–10 days) in alanine aminotransferase and/or aspartate aminotransferase were observed in three patients (0.4%) receiving atorvastatin 10 mg and seven patients (0.9%) receiving atorvastatin 80 mg.</p> <p>There were no significant differences</p>
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								between the treatment groups in the rate of treatment-related adverse events, including myalgia, or persistent elevations in liver enzymes. No incidents of rhabdomyolysis were reported in either treatment group with diabetes.	
Berne C, Siewert DA, URANUS si. Comparison of rosuvastatin and atorvastatin for lipid lowering in patients with type 2 diabetes mellitus: results from the URANUS study. Cardiovascular Diabetology 2005; 4:7, 2005 Jun 3.:7, 2005. Ref ID: 3396	RCT double blind multicentre parallel-group study conducted in 51 centres in Sweden.  1+	N= 465	Inclusion criteria: Patients (male or female) aged 18 years or more were eligible for the study if they had a history of T2D for at least 3 months; were being treated with diet, oral antidiabetic medication, insulin or a combination of these treatments; and had fasting LDL-C of $\geq 3.3$ mmol/L and triglycerides (TG) of $<6.0$ mmol/L at enrolment.  Exclusion criteria included: type 1 diabetes; uncontrolled type 2 diabetes; uncontrolled hypothyroidism or hypertension; nephrotic syndrome or severe renal failure; active liver disease or hepatic dysfunction; active arterial disease (e.g., unstable angina, myocardial infarction, transient ischaemic attack, cerebrovascular accident, coronary artery bypass grafting or	Rosuvastatin 10 mg (N = 232) For 4 weeks  Titrated up to 40mg over 12 weeks to achieve the 1998 European LDL-C goal ( $<3.0$ mmol/L).	Atorvastatin 10 mg (N= 233) For 4 weeks  Titrated up to 80mg over 12 weeks to achieve the 1998 European LDL-C goal ( $<3.0$ mmol/L).	16 weeks	<u>Primary endpoint:</u> percentage change in LDL from baseline to 16 weeks  <u>Secondary endpoint:</u> percentage change in LDL from baseline to 4 weeks; percentage of patients achieving the 1998 European LDL goal at 4 and 16 weeks; percentage change in TC, TG, HDL from baseline to 4 and 16 weeks; and the number of titration steps at 16 weeks.  <u>Tertiary endpoint:</u> the difference in overnight urinary albumin	*Primary endpoint At the end of the titration-to-goal period (week 16) rosuvastatin was significantly more effective than atorvastatin on the primary efficacy measure, reducing LDL by 52% compared with 46% in the atorvastatin group. Difference 95% CI -6.7 (-8.8 to -4.7) $p < 0.0001$  *Secondary endpoint At 16 weeks, significantly more patients achieved their LDL goal with rosuvastatin compared with atorvastatin (94% vs 88%, $p < 0.05$ ) Furthermore, more patients achieved the goal on the starting dose of rosuvastatin than atorvastatin (75% vs 54%)  During the 4-week fixed-dose period, significantly more patients on rosuvastatin 10 mg had reached the 1998 European LDL-C goal compared with patients on atorvastatin 10 mg (81% vs 65%, $p < 0.001$ ).  When data from the fixed-dose period were re-analysed to the more stringent 2003 European LDL-C goal of $<2.5$ mmol/L, 65% of patients receiving rosuvastatin 10 mg achieved goal compared with 33% of patients receiving atorvastatin 10 mg	AstraZeneca

			<p>percutaneous transluminal coronary angioplasty within 3 months before beginning the study); serum creatinine kinase (CK) levels &gt;3 × the upper limit of normal (ULN); body mass index &gt;35 kg/m<sup>2</sup>; and known hypersensitivity to statins.</p> <p>The two groups were well matched at baseline</p>				<p>excretion (UAE) from baseline to 16 weeks.</p> <p><u>Safety issues</u></p>	<p>(p &lt; 0.001)</p> <p>At 4 weeks, 65% of rosuvastatin patients had reached their 2003 European LDL goal (&lt; 2.5 mmol/L), compared with 33% of atorvastatin patients (p &lt; 0.0001)</p> <p>At 4 weeks Rosuvastatin also reduced TC, LDL/HDL ratio, and TC/HDL ratio significantly (p &lt; 0.0001) more than atorvastatin</p> <p>Both treatments increased HDL and decreased Tg from baseline to 4 weeks, but there were no statistically significant differences between the groups.</p> <p>Tertiary endpoint:: There was no statistically significant difference in UAE rate from baseline to study end, or between the treatment groups, including those patients with baseline microalbuminuria (UAE &gt;20 µg/min).</p> <p>* Safety issues Both treatments were well tolerated, with overall incidences of adverse events being similar between the treatment groups (51% with rosuvastatin, 53% with atorvastatin). A total of 10 patients experienced serious adverse events (two in the rosuvastatin group, eight in the atorvastatin group), none of which were considered by the investigator to be related to study treatment.</p> <p>Ten patients discontinued because of adverse events, three in the</p>	
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								<p>rosuvastatin group and seven in the atorvastatin group.</p> <p>There were no cases of myopathy. Myalgia was reported by 3.4% of the patients in the study; none of the cases were associated with a clinically important elevation in CK (&gt;5 × ULN).</p> <p><b>Adverse events occurring in ≥ 3% of patients in any treatment group</b></p> <table border="1"> <thead> <tr> <th></th> <th>R</th> <th>A</th> </tr> </thead> <tbody> <tr> <td>Nasopharyngitis</td> <td>23 (9.9)</td> <td>19 (8.1)</td> </tr> <tr> <td>Myalgia</td> <td>13 (5.6)</td> <td>7 (3.0)</td> </tr> <tr> <td>Constipation</td> <td>9 (3.9)</td> <td>6 (2.5)</td> </tr> <tr> <td>Headache</td> <td>6 (2.6)</td> <td>7 (3.0)</td> </tr> <tr> <td>UTI</td> <td>9 (3.9)</td> <td>2 (0.9)</td> </tr> <tr> <td>Arthralgia</td> <td>1(0.4)</td> <td>9 (3.8)</td> </tr> </tbody> </table>		R	A	Nasopharyngitis	23 (9.9)	19 (8.1)	Myalgia	13 (5.6)	7 (3.0)	Constipation	9 (3.9)	6 (2.5)	Headache	6 (2.6)	7 (3.0)	UTI	9 (3.9)	2 (0.9)	Arthralgia	1(0.4)	9 (3.8)	
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<p>Miller M, Dobs A, Yuan Z, Battisti WP, Borisute H, Palmisano J. Effectiveness of simvastatin therapy in raising HDL-C in patients with type 2 diabetes and low HDL-C. Current Medical Research &amp; Opinion 2004; 20(7):1087-1094. Ref ID: 3411</p>	<p>RCT double blind, 3-period, complete block, 6-week cross over study</p> <p>1+</p>	N=151	<p>Inclusion criteria: men and women ages 18 through 75 years with stable T2D (HbA1c&lt;9% LDL &gt; 100mg/dL (2.6mmol/L), HDL &lt;40mg/dL (&lt;1mmol/L), and fasting Tg level &gt;150mg/dL (&gt;1.7mmol/L) and &lt;700mg/dL (&lt;7.9mmol/L) were eligible.</p> <p>Exclusion criteria: Patients with renal insufficiency (serum Cr&gt;1.8mg/dL), hepatic transaminase levels &gt;30% above the upper limit of normal, patients with uncontrolled</p>	simvastatin 80 mg	simvastatin 40 mg  Placebo	6 weeks	<p>Lipid profile</p> <p>Safety issues</p>	<p>Lipid profile (LDL – Tg)</p> <p>Both doses of simvastatin 80mg and simvastatin 40mg significantly reduced both LDL (47% and 41% respectively) from baseline (mean: 132 ± 38mg/dL; 3.5 ± 1.0mmol/L) as well as Tg (31% and 29%, respectively; baseline median: 273mg/dL; 3.1 mmol/L)</p> <p>Simvastatin 80mg treatment provided additional efficacy compared with simvastatin 40mg in reducing LDL, TG. After a 6-week treatment, approximately 87% (104/119) of patients treated with simvastatin 80mg, and 82% (96/117) of patients treated with simvastatin 40mg, had LDL values that met or exceeded the NCEP ATP III treatment goal of &lt; 100mg/dl (2.6 mmol/L), compared with only 14.3 (17/119) of patients treated with placebo.</p>	Merck																					

			hypertension or a history of recent acute coronary syndrome.					<p>HDL</p> <p>At 6 weeks, both simvastatin 80mg and 40mg significantly increased HDL from the baseline mean of 34 ±5 (SD) mg/dl (90 mmol/L). Simvastatin 80mg increased HDL by 8% from baseline compared with a 0.4% decrease for placebo treatment (difference of 9%, p5% CI: 7-11%, p&lt;0.001); simvastatin 40mg significantly increased HDL by 5% from baseline compared with placebo (difference of 5%; 95% CI 3-7% p&lt;0.001). The comparison between simvastatin 80mg and simvastatin 40mg was also statistically significant (difference of 4% p5%CI 1-6%; p=0.001) favouring simvastatin 80mg.</p> <p><u>Safety</u></p> <p>Overall clinical as adverse events by treatment period were similar for simvastatin 80mg (32.2%), simvastatin 40mg (32.9%), and placebo (29.2%). No drug-related serious clinical AEs were observed. Two patients on simvastatin 80mg treatment had an ALT and AST level &gt; 3 times the upper limit of normal; on of these patients was discontinued because of these elevations (the liver function tests returned to normal after discontinuation of the therapy)</p>	
Sever PS, Poulter NR, Dahlof B, Wedel H, Collins R, Beevers G et al. Reduction in cardiovascular events with atorvastatin in 2,532 patients with	Post-hoc analysis of ASCOT-LLA  RCT double	N= 2,532 with T2D	Inclusion criteria: Patients eligible for inclusion in ASCOT were men and women with hypertension aged 40–79 years at randomization. Study	Atorvastatin <sup>7</sup> 10mg/day	Placebo	3.3 years (median follow-up) <sup>8</sup>	<u>Primary composite endpoint:</u> Total cardiovascular events and procedures included the	* Primary endpoint <sup>9</sup> There were 116 (9.2%) major cardiovascular events or procedures in the atorvastatin group and 151 (11.9%) events in the placebo group (hazard ratio 0.77, 95% CI 0.61 to 0.98; p<0.036) <sup>10</sup>	Pfizer

<p>type 2 diabetes: Anglo-Scandinavian Cardiac Outcomes Trial--lipid-lowering arm (ASCOT-LLA). Diabetes Care 2005; 28(5):1151-1157. Ref ID: 3410 <sup>6</sup></p>	<p>blind multicentre 1+</p>		<p>participants were required to have at least three of the following risk factors: type 2 diabetes, male sex, age <math>\geq 55</math> years, microalbuminuria or proteinuria, smoking, ratio of plasma total cholesterol to HDL cholesterol <math>\geq 6</math>, premature family history of CHD, left ventricular hypertrophy, other specified abnormalities on electrocardiogram, peripheral arterial disease, previous stroke, or transient ischemic attack.</p> <p>Exclusion criteria: included previous MI, currently treated angina, a cerebrovascular event within the previous 3 months, fasting</p>			<p>following diagnoses: cardiovascular mortality, nonfatal MI (symptomatic plus silent), unstable angina, chronic stable angina, life-threatening arrhythmias, nonfatal heart failure, nonfatal stroke, peripheral arterial disease, retinal vascular thrombosis, revascularization procedures, transient ischemic attacks, and reversible ischemic</p>	<p>For the individual components of this composite end point, the number of events occurring in the diabetes subgroup was small. Therefore, although fewer coronary events (0.84, 0.55 to 1.29; <math>p=0.14</math>) and strokes (0.67, 0.41 to 1.09; <math>p=0.66</math>) were observed among the patients allocated atorvastatin, these reductions were not statistically significant.</p> <p>In the total ASCOT-LLA population, the primary end point of nonfatal myocardial infarction and fatal CHD was reduced by 36% (<math>p&lt;0.0005</math>). Among the diabetic subgroup, the observed 16% risk reduction was not statistically significant, but only 84 such first events occurred among these diabetic participants; the proportional reduction was not significantly different from the reduction among the nondiabetic participants.</p> <p>*Lipid profile</p>	
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<sup>6</sup> ASCOT is a multicentre trial designed to compare two antihypertensive treatment strategies for the prevention of coronary heart disease (CHD) events in 19,342 hypertensive patients who have no history of CHD. In a two-by-two factorial design, ASCOT included a double blind randomized comparison of the cardiovascular effects of atorvastatin with placebo among 10,305 patients who had total cholesterol concentrations  $<6.5$  mmol/l. This report presents a detailed analysis of the 2,532 diabetic participants whose investigation was a pre-specified subsidiary aim of the trial.

<sup>7</sup> Patients were also randomly assigned one of two antihypertensive regimens. At each follow-up visit, antihypertensive drug therapy was titrated to achieve target blood pressures ( $<140/90$  mmHg for nondiabetic patients and  $<130/80$  mmHg for diabetic patients); information was recorded about adverse events and any new cardiovascular event or procedure, including the cause for any hospital admission. Information on potential end points was reviewed by a blinded end point committee.

<sup>8</sup> ASCOTLLA was stopped prematurely after a median follow-up of 3.3 years on the grounds that atorvastatin had resulted in a highly significant reduction in the primary end point of fatal CHD events and nonfatal myocardial infarction.

<sup>9</sup> The effect of atorvastatin on total cardiovascular events and procedures in the diabetic subgroup was unaffected by baseline cholesterol concentration. The HRs were 0.72 (95% CI 0.44 to 1.18), 0.74 (0.52 to 1.05), and 0.84 (0.54 to 1.31) for those with baseline cholesterol concentrations of  $<5.0$ , 5.0 to  $<6.0$ , and  $\geq 6.0$  mmol/l, respectively.

<sup>10</sup> Even excluding 306 diabetic people with some other pre-existing cardiovascular disease, there was still a significant reduction in total cardiovascular events and procedures of 25% (95% CI 0.57 to 0.99;  $p<0.038$ ) among the remaining 2,226 diabetic patients.

			<p>triglyceride level &gt;4.5 mmol/l, heart failure, uncontrolled arrhythmias, or any clinically important haematological or biochemical abnormality on routine screening. Eligibility for ASCOT-LLA also required a total cholesterol concentration <math>\leq</math>6.5 mmol/l and no current use of a statin or fibrate.</p> <p>Baseline characteristics of participants in these two randomized groups were well matched.</p>				<p>neurological deficits.</p> <p><u>Lipid profile</u></p> <p><u>Safety issues</u></p>	<p>Among diabetic participants in the atorvastatin group, total cholesterol and calculated LDL cholesterol levels at year 1 of follow-up were lower than in the placebo group by ~1.3 and 1.2 mmol/l, respectively. By the end of the study, these differences were 0.9 and 0.9 mmol/l, respectively.</p> <p>In those allocated atorvastatin compared with placebo, triglyceride levels were lowered by 0.3 mmol/l after 1 year and 0.2 mmol/l at study completion. Changes in HDL cholesterol concentration were minimal in both groups.</p> <p>* Other outcomes Blood pressure control throughout the trial was similar in diabetic patients assigned atorvastatin and placebo, with mean values at the end of follow-up of 138.5 mmHg systolic and 77.7 mmHg diastolic and 138.4 mmHg systolic and 77.3 mmHg diastolic, respectively. Body weight, fasting blood glucose, and creatinine were well matched at baseline and were unaltered in either group by the time of close out.</p> <p>*Safety issues The use of atorvastatin in the diabetic population was not associated with any excess risk of adverse reactions, and there were no significant differences in liver enzyme abnormalities between those allocated statin and placebo. No cases of rhabdomyolysis were reported.</p>	
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van Venrooij FV, van de Ree MA, Bots ML, Stolk RP, Huisman MV, Banga JD et al. Aggressive lipid lowering does not improve endothelial function in type 2 diabetes: the Diabetes Atorvastatin Lipid Intervention (DALI) <sup>11</sup> Study: a randomized, double-blind, placebo-controlled trial. Diabetes Care 2002; 25(7):1211-1216. Ref ID: 437	Post-hoc analysis of DALI study  RCT double blind 1+	N= 133	Inclusion criteria: men and women aged 45–75 years with HbA1c ≤10% were eligible. Lipid inclusion criteria were total cholesterol between 4.0 and 8.0 mmol/l and fasting triglycerides between 1.5 and 6.0 mmol/l.  The baseline characteristics of the subset of 133 patients who entered the flow mediated vasodilation (FMD) protocol were similar with the exception of patients randomized to placebo who had higher BMI. No significant associations were found between endothelial function and lipid variables at baseline	Atorvastatin 10mg	Atorvastatin 80mg`  Placebo	30 weeks	Endothelial function  Lipid profile	Both standard and aggressive therapy with atorvastatin did not affect FMD. After 30 weeks, the mean FMD was 3.20±0.48 and 3.10±0.42% in A10 and A80, respectively, versus 3.41 ±0.46% in the placebo group (p>0.8) <b>(not relevant to the Q)</b>  Lipid profile Atorvastatin treatment effectively reduced all atherogenic lipid parameters and increased HDL cholesterol  LDL After 30 weeks, LDL cholesterol (SD) was reduced to 2.0 mmol/l (0.5) (-46%; p<0.001) in A10 and 1.8 mmol/l (1.0) (-51%; p<0.001) in A80 (A80 versus A10; p< 0.01)  Tg Fasting triglyceride levels were reduced to 1.76 mmol/l (0.74) (-29%; p<0.001) in A10 and 1.61 mmol/l (1.0) (-43%; p<0.001) in A80.  HDL HDL cholesterol was increased to 1.12 mmol/l (0.3) in A10 and 1.10 mmol/l (0.3) in A80 (both +6%; p< 0.005).	Parke-Davis
Insull W, Kafonek S, Goldner D, Zieve F. Comparison of efficacy and safety of atorvastatin (10mg) with simvastatin	RCT multicentre open label  1-	N= 1,424 patients  N= 666 diabetics	Inclusion criteria:  study participants were men and women with mixed dyslipidaemia, 18 to 80 years old, with our	Atorvastatin 10mg  N= 730	Simvastatin 10mg  N= 694	6 weeks	Primary endpoints  * Mean % change in LDL from baseline	<u>Primary endpoints</u>  * Mean % change in LDL from baseline  Both treatment groups had significant	Not reported

<sup>11</sup> The study on endothelial function comprised a subset of the 217 patients with diabetes enrolled in the Diabetes Atorvastatin Lipid Intervention (DALI) study.

<p>(10mg) at six weeks. ASSET Investigators. American Journal of Cardiology 2001; 87(5):554-559. Ref ID: 3415</p>			<p>without CHD/peripheral vascular disease, and with or without type 2 diabetes. To be eligible for randomization, patients were to have a mean fasting triglyceride value of 200 to 600 mg/dl (2.26 to 6.77 mmol/L) calculated from weeks -4 and -2, and a mean LDL cholesterol level at weeks -4 and -2 as follows: &lt;2 NCEP risk factor for CHD, 190 to 350 mg/dl (4.91 to 9.05 mmol/L); ≥ 2 risk factors for CHD, 160 to 300 mg/dl (4.14 to 7.76 mmol/L); clinically evident CHD or peripheral vascular disease, 130 to 250 mg/dl (3.36 to 6.46 mmol/L). Exclusion criteria: pregnant or breastfeeding; known hypersensitivity to statins; uncontrolled hypothyroidism, nephrotic syndrome or renal dysfunction; T1D or uncontrolled T2D (HbA1c &gt;10% at week -4); history of ketoacidosis, hepatic dysfunction, creatine phosphokinase levels &gt;</p>				<p>* overall % of patients who reached their NCEP LDL treatment goal for the combined risk categories.<sup>12</sup>  Secondary endpoints  * TC, HDL, Tg  *Safety profile</p>	<p>% decreases in LDL from baseline, although the decrease observed with atorvastatin (37.2%) was significantly greater (p&lt;0.0001).  * Overall % of patients who reached their NCEP LDL treatment goal  The overall % of patients achieving the NCEP LDL goal for the combined risk categories was significantly greater (p&lt;0.0001) in the atorvastatin group (55.6%) than in the simvastatin (38.4%) group.  <u>Secondary endpoints</u>  Atorvastatin-treated patients had nonsignificant (p=0.38) increases from baseline in HDL compared with simvastatin-treated (7.4% vs 6.9%), and significantly greater (p&lt;0.0001) decreases from baseline in total cholesterol (27.6% vs 21.5%), triglycerides (22.1% vs 16.0%)  <u>Subgroup analysis</u> Superior lipid lowering efficacy of atorvastatin versus simvastatin was observed both in patients with and without T2D. within each treatment group.  However, atorvastatin compared with simvastatin produced a significantly greater reduction in LDL cholesterol in patients both with (37.1% vs 29.7%; p&lt;0.0001) and without (37.3% vs 29.5%, p&lt;0.0001) diabetes.</p>	
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<sup>12</sup> For patients with <2 risk factors for CHD, the LDL treatment goal was <160mg/dl (<4.14 mmol/L), whereas for patients with ≥2 CHD risk factors, the goals was <130mg/dl (<3.36 mmol/L), and for patients with established CHD/peripheral vascular disease, ≤100mg/dl (≤2.59 mmol/L)

			3 times the upper limit of normal, MI, revascularization procedures, or severe or unstable angina within 1 month before screening.				<u>Safety profile</u>  At week 6, there was no difference between the 2 treatment groups in the % of patients reporting adverse events. The proportion of patients having treatment-associated adverse events was 5.8% in the atorvastatin group and 2.9% in the simvastatin group.  The proportion of patients having treatment-associated adverse events was 5.8% in the atorvastatin group and 2.9% in the simvastatin group (most of them mild or moderate). Less than 1% in either group withdrew due to treatment –associate adverse events.	
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