

### Evidence Tables

## NICO 1: Are nicotinic acid derivatives 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
Elam MB HDDKG. Effect of niacin on lipid and lipoprotein levels and glycemic control in patients with diabetes and peripheral arterial disease: the ADMIT study: A randomized trial. Arterial Disease Multiple Intervention Trial. JAMA : the journal of the American Medical Association 2000; 284(10):1263-1270. Ref ID: 272	RCT multicentre, double blind  1++	N= 125 <sup>1</sup>	Inclusion criteria: ADMIT participants had either a reduced ankle brachial index of less than 0.85 or a history of prior lower-extremity revascularization. 125 ADMIT enrollees met study criteria for diabetes at the first study visit. Diabetes was defined as either a history of diabetes treated by diet or medication or HbA1c higher than 7% at the baseline visit.  Exclusion criteria included: poorly controlled diabetes (HbA1c>9.0%), a history of diabetic ketoacidosis or coma,. Participants with	Niacin 3,000 mg/d N=64	Placebo N=61	48 weeks <sup>2</sup>	Lipid profile Glycaemic effects	<b>Lipid profile</b> *HDL Niacin therapy significantly increased HDL by 29% compared to 0% increase in placebo treated patients. (p<0.001)  *LDL Niacin significantly decreased LDL levels by 8% compared to an increase of 1% in patients taking placebo (p<0.001)  * Triglycerides Niacin therapy significantly decrease Tg levels by 23% compared to an increase of 7% in placebo-treated patients (p<0.001)  <b>Glycaemic effects</b> <sup>3</sup> *HbA1c Level of HbA1c were unchanged from baseline to follow-up in participants treated with niacin. However, in placebo-treated patients HbA1c decreased by 0.3% (p=0.04)	Academics (& university of Tennessee) and Public sector (National Heart, Lung and Blood institute)

<sup>1</sup> Of 468 ADMIT participants, 125 patients with diabetes were included. This paper describes the effect of niacin treatment on plasma lipoproteins and glycemic status in ADMIT participants with diabetes

<sup>2</sup> Preceded by an 12-week active niacin run-in period, during which crystalline (immediate release) niacin tablets were dispensed at 4-week intervals in increasing doses of 50,250, and 500mg twice daily.

<sup>3</sup> The protocol specified down-titration of niacin if HbA1c level exceeded 10%. This HbA1c limit was exceeded after randomization in 18 participants, 10 of whom were assigned to niacin and 8 assigned to placebo.

			marked hypertriglyceridaemia (>400 mg/dl) for whom randomization to niacin placebo would not have been appropriate, or whose LDL level was not likely to be controlled by niacin and/or pravastatin (LDL > 190mg/dl) were also excluded from participation.					<p>*Fasting glucose Niacin use resulted in a small but statistically significant increase in average glucose levels (8.1 mg/dl) compared with a decrease of 8.7 mg/dl in those patients receiving placebo. (p=0.04)</p> <p><b>Adverse events</b> Niacin increased uric acid levels over baseline values (from 339umol/l to 386umol/l). No change was seen in placebo-treated patients (p&lt;0.001)</p> <p>Discontinuation Niacin discontinuation was comparable in participants randomized to receive active niacin and placebo (23% vs 18% respectively; p=0.46)</p> <p>Glucose intolerance was listed as the reason for niacin discontinuation in 4 participants (6%) who were randomized to active niacin and in 2 randomized to placebo (p=0.44)</p> <p>Other reasons for discontinuation of niacin included comorbid vascular disease, patient request, and acanthosis nigricans.</p>	
A. Garg and S. M. Grundy. Nicotinic acid as therapy for dyslipidemia in non-insulin-dependent diabetes mellitus.[see	RCT, crossover, non-blinded  1+	N=13, single centre, USA	Inclusion: Men, 49-68yrs, BMI 29.9±0.7kg/m2, weight 91.7±3.3kg. all T2D, 4 taking glyburide, 8 taking insulin, 1 diet therapy only. Plasma cholesterol ≤5.2mmol/L,	N=13 Either nicotinic acid 1.5g TID or not therapy (control), crossover	N=13 Either nicotinic acid 1.5g TID or not therapy (control)	16 weeks, 5 days  5 days baseline to achieve good glycaemic	Plasma cholesterol, plasma triglycerides, VLDL cholesterol, LDL cholesterol,	<p>Analysis of variance did not reveal any differences in the response to nicotinic acid therapy whether patients received insulin, glyburide, or no hypoglycaemic drugs, therefore values in patients were pooled.</p> <p>* Lipids</p>	Veterans Administration, NIH, Southwestern Medical

<p>comment]. <i>JAMA</i> 264 (6):723-726, 1990.</p>			<p>plasma triglyceride <math>\leq 2.8</math> mmol/L.  Exclusion: peptic ulcer or gout, hyperuricaemia (plasma uric acid <math>&gt; 475 \mu\text{mol/L}</math>), abnormal liver, kidney or thyroid functions.</p> <p>Any participants taking specific hypolipidaemic drugs discontinued at least 2 months prior to the study.</p> <p>NOTE: prior to randomisation patients were hospitalised and insulin or glyburide adjusted to achieve good glycaemic effect, thereafter no changes to in the dosages were allowed except to prevent symptomatic hypoglycaemia.</p>	<p>Nicotinic acid dosage was gradually increased from 50mg TID on the first day to 1.5gTID by the end of the third week, then a constant dose of 1.5g TID was taken for 5 weeks</p>	<p>NOTE: All patients were instructed to follow an isocaloric diet throughout the study</p>	<p>control, 8 weeks drug/no therapy, crossover, 8 weeks drug/no therapy</p>	<p>HDL cholesterol, total cholesterol/ HDL cholesterol ratio, plasma glucose, 24h plasma glucose profile, glycosylated haemoglobin, 24h urinary glucose, plasma uric acid, body weight</p>	<p>Compared with the control period nicotinic acid had significant reductions in: plasma cholesterol (<math>P &lt; 0.0001</math>), plasma triglyceride levels (<math>p = 0.0006</math>), VLDL cholesterol (<math>p = 0.0009</math>) and an increase in HDL cholesterol (<math>p = 0.0001</math>). LDL cholesterol decrease was non significant. The total cholesterol and HDL cholesterol ratio also decreased significantly with nicotinic acid compared with the control period (<math>p = 0.0001</math>).</p> <p>*Glycaemic effects  The daily requirements of hypoglycaemic drugs did not change in 10/13 participants.  There was a non-significant increase of 16% in mean plasma glucose levels from 7.8 to 9.1 mmol/L from control to nicotinic acid.  Compared with the control period there was a significant increase in 24h plasma glucose profile (<math>p = 0.047</math>), in glycosylated haemoglobin (<math>p = 0.002</math>), 24h urinary glucose (<math>p = 0.016</math>) and plasma uric acid (<math>p = 0.0001</math>).</p> <p>*Adverse events  In 2 participants mean plasma uric acid values rose to very high levels 684 and 761 <math>\mu\text{mol/L}</math>.  Minor complaints of flushing.  Headaches (N=1)</p> <p>*Discontinuation  No participants discontinued due to adverse events</p>	<p>Foundation, Moss Heart Foundation</p>
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<p>Grundy SM VGMMTBKDF-P. Efficacy, safety, and tolerability of once-daily niacin for the treatment of dyslipidemia associated with type 2 diabetes: results of the assessment of diabetes control and evaluation of the efficacy of niaspan trial. Archives of internal medicine 2002; 162(14):1568-1576. Ref ID: 3288</p>	<p>RCT double blind, multicentre  1+</p>	<p>N=148  ITT population: 146</p>	<p>Inclusion criteria: subjects 21 years or older with stable T2D (FBG no greater than 200mg/dl and an hbA1c no greater than 9%) with a history of diabetes controlled by diet, oral hypoglycaemic agent (except glitazones) or insulin. Lipid level variables for inclusion were based on treatment status. All of the patients had 1 or more of the following lipid characteristics: an LDL level of at least 130mg/dl; an HDL level of no greater than 40mg/dl; or a TG level of at least 200mg/dl.  The groups were generally well balanced. However, significant differences in weight, BMI, and HDL levels were found among treatment groups (p&lt;0.001) with patients in the 1000mg ER</p>	<p>Niacin ER (extended-release) 1000mg/d N= 47  Niacin ER (extended-release) 1500mg/d N=52  Titration <sup>4</sup></p>	<p>Placebo N=49</p>	<p>16 weeks</p>	<p>Lipid profile Glycaemic effects <sup>5</sup> Adverse events</p>	<p><b>Lipid profile</b> HDL Dose-dependent increases in HDL (+19% to +24% [p&lt;0.05] vs placebo for both niacin dosages)  At week 16, the mean absolute increases in HDL were 1.6mg/dl, 7.6 mg/dl, and 11.0 mg/dl in the placebo and 1000 and 1500mg ER niacin groups respectively  Tg Dose-dependent reduction in triglyceride levels (-13% to -28% [p&lt;0.05] vs placebo for the 1500mg ER niacin) were observed.  The median % of change from baseline in the placebo group were small, ranging from -5 to -8%. In the 1000mg ER niacin group, the median % of change ranged from -15% to -20% these changes were not significantly different from those in the placebo group.  *LDL In the 1500mg ER niacin group, LDL levels decreased at all time points, and the difference compared with placebo group was statistically significant at</p>	<p>Kos - Pharmaceutical</p>
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<sup>4</sup> Titration:

For the first 4 weeks of treatment, the dosage of ER niacin was escalated as follows. During week 1, patients received 375mg/d of ER niacin (or matching placebo); during week 2, 500mg/d of ER niacin (or matching placebo); during week 3, 750 mg/d of ER niacin (or matching placebo); and during week 4, 1000 mg/d of ER niacin as two 500mg tablets (or matching placebo). Thereafter, subjects randomized to the 1000mg/d group received two 500 tablets once a day at bedtime through week 16. subjects randomized to receive 1500mg/d received two 750mg tablets once a day at bedtime through week 16.

<sup>5</sup> The investigator could adjust the dosage of any concomitant antidiabetic pharmacotherapy during the trial as needed to maintain glycemic control, based on the standard of practice at each centre.

			<p>niacin group having higher baseline TG and HDL levels. These patients also tended to have higher baseline TG and FBG levels.</p>				<p>week 12 and 16 (p&lt;0.05)</p> <p>The mean changes from baseline at 16 weeks were +9%, +5%, and -7% in the placebo and 1000 and 15000mg ER niacin groups respectively.</p> <p><b>*Total Cholesterol</b> The mean changes from baseline at 16 weeks were +4%, +4%, and -6% in the placebo and 1000 and 15000mg ER niacin groups respectively. (non statistical analysis reported)</p> <p>* TC/HDL ratio favoured both dosages of ER niacin, with mean changes at week 16 in the 1000 1500mg ER niacin groups of -12% and -22%, respectively, which were significantly different from those of the placebo group (p&lt;0.01)</p> <p><b>Glycaemic effects</b> <b>*HbA1c</b> Baseline and week 16 values for HbA1c were 7.13% and 7.11%, respectively, in the placebo group; 7.28% and 7.35%, respectively, in the 1000mg ER niacin group (p=0.16 vs placebo); and 7.2% and 7.5%, respectively, in the 1500mg ER niacin group (p=0.048 vs placebo)</p> <p><b>Adverse Events</b> No statistically significant differences among the 3 treatment groups in the incidence of any individual AE, except for flushing were reported.</p> <p>Flushing was reported at some time</p>	
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								<p>during the trial by 2/3 of patients receiving ER niacin and by approx 10% of patients receiving placebo.</p> <p>No significant differences in uric acid levels were found at any time point across groups.</p> <p>No patient in the study experienced elevation of liver enzyme levels of greater than 3 times the upper limit of the reference range.</p> <p><b>Discontinuation</b> 25 patients were discontinued from the study prematurely, 7 (14%) in the placebo group, 8 (18%) in the 1000mg ER niacin group and 10 (19%) in the 1500mg ER niacin group.</p> <p>Four patients dropped out because of inadequate glucose control (1 in the 1000mg ER niacin group and 3 in the 1500mg ER niacin group). Adverse events were responsible for 5 (10%), 3 (7%), and 7 (13%) patients discontinuing in the placebo and 1000 and 1500 mg ER niacin groups, respectively.</p> <p>Four patients discontinued participation in the study because of flushing, including 1 in the placebo group.</p>	
C. Tsalamandris, S. Panagiotopoulos, A. Sinha, M. E. Cooper, and G. Jerums. Complementary	RCT, appears to be non-blinded, pravastatin and	N=44 N=33, used for analysis (N=22 non diabetics)	Inclusion criteria: aged 20-70yrs, total cholesterol of $\geq 6.5$ mmol/L and triglycerides of $\geq 2.5$ mmol/L after dietary	N=15, nicotinic acid 1500mg/day  Nicotinic acid dosage	N=18 pravastatin 40mg/day	32 weeks  8 week run-in, 12 week nicotinic acid/pravast	Total cholesterol, triglyceride, LDL cholesterol, HDL	NOTE: there was no difference in the change in lipid levels between diabetic and non diabetic patients receiving combination therapy. Data for the efficacy was given for the total sample – for the glycaemic effects	Bristol-Myers Squibb

<p>effects of pravastatin and nicotinic acid in the treatment of combined hyperlipidaemia in diabetic and non-diabetic patients. <i>Journal of Cardiovascular Risk</i> 1 (3):231-239, 1994.</p>	<p>nicotinic acid, followed by a combination phase</p> <p>1+</p>	<p>and N=11 T2D), single centre, Australia</p>	<p>modification. Exclusion criteria: those with type I, IIA, III, IV or V hyperlipaemia, HDL <math>\geq 2.0</math>mmol/L, type 1 diabetes, recent cardiovascular disease, using drugs prohibited by the study, renal disease, liver disease, chronic pancreatitis, hypothyroidism, obesity, alcohol abuse</p> <p>Groups were similar at baseline, though diabetic participants were older than the non diabetic participants (61.8<math>\pm</math>2.5 and 52.0<math>\pm</math>2.6, p=0.02)</p> <p>NOTE: 8 weeks before randomisation participants stopped any hypolipidaemic medication and commenced a standard lipid lowering diet. Patients were entered into the study if their total cholesterol and triglyceride levels were still elevated at week 0</p>	<p>was titrated: week 1, 250mg/day; week 2, 500mg/day; week 3, 750mg/day; from week 4 onwards 1500mg/day</p> <p>Followed by the entry of all participants into a combination therapy phase of pravastatin 20mg/day and nicotinic acid 1000mg/day (titrated; week 1, 250mg/day, week 2, 500mg/day, week 3 onwards 1000mg/day )</p>	<p>NOTE: Aspirin (150mg/day) was prescribed for all those taking nicotinic acid and was to be used if flushing was significant</p>	<p>atin phase, 12 week combination phase</p>	<p>cholesterol, lipoprotein-(a), glycosylated haemoglobin, fasting plasma glucose, adverse events</p>	<p>the data was presented for the diabetic and non-diabetic groups.</p> <p>*Total cholesterol Pravastatin monotherapy showed significantly greater reductions in total cholesterol compared with nicotinic acid (-24.9<math>\pm</math>2.0 vs -9.8<math>\pm</math>2.9, p&lt;0.001). Combination therapy showed a significantly greater reduction in total cholesterol compared with nicotinic acid (-23.8<math>\pm</math>2.9 vs -9.8<math>\pm</math>2.9, p&lt;0.001). there was no significant difference in the reductions with pravastatin and combination therapy.</p> <p>*Triglycerides The reduction in triglyceride levels was equivalent for pravastatin and nicotinic acid as monotherapy. Combination therapy showed significant reductions in triglyceride levels compared with both nicotinic acid (-39.4<math>\pm</math>6.7 vs -31.8<math>\pm</math>6.8, p=0.03) and pravastatin (-39.3<math>\pm</math>5.4 vs -28.0<math>\pm</math>5.1, p=0.01).</p> <p>*HDL cholesterol Nicotinic acid showed greater increases in HDL cholesterol than pravastatin, these were not significant. Combination therapy did not show significantly greater increases in HDL cholesterol than nicotinic acid but did find significantly greater increase when compared with pravastatin (35.6<math>\pm</math>4.1 vs 16.4<math>\pm</math>5.8, p&lt;0.001).</p>	
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								<p>*LDL cholesterol (means of 21/33 participants data unavailable for the remaining)  Pravastatin showed greater decreases in LDL cholesterol compared with nicotinic acid (-32.1±3.0 vs -16.9±3.3, p&lt;0.01).  Combination therapy showed significantly greater decreases in LDL cholesterol compared with nicotinic acid (-35.7±3.3 vs -16.9±3.3, p&lt;0.01).</p> <p>*Lipoprotein-(a)  Levels of lipoprotein (a) were not significantly changed by any of the treatments</p> <p>*Glycaemic effects - Diabetic participants  There was no change for those receiving pravastatin.  Nicotinic acid monotherapy increased HbA1c levels by approx. 8%, p=0.03, and increased fasting plasma glucose levels by approx 26%, p=0.02.  Combination therapy showed a non significant increase in glycosylated haemoglobin and no change on fasting plasma glucose.</p> <p>*Glycaemic effect – non diabetic participants  Pravastatin showed no change in levels.  Nicotinic acid monotherapy increased HbA1c levels by approx 4%, p=0.02.  Combination therapy caused an increase of approx 6%, p&lt;0.01.  None of the treatments significantly</p>
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								<p>increased fasting plasma glucose levels.</p> <p>*Adverse events and discontinuation From the starting 44 participants, during the trial period nine patients had significant flushing or nausea with nicotinic acid and withdrew from the trial, 9/44, 21%. One participant in the pravastatin group withdrew with nausea. One participant with previous ischaemic heart disease, died during the trial from pulmonary oedema.</p>	
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