## HPS2-THRIVE: Randomized placebo-controlled trial of ER niacin and laropiprant in 25,673 patients with pre-existing cardiovascular disease.

Jane Armitage on behalf of the HPS2-THRIVE Collaborative Group

<u>Financial Disclosure</u>: Grant to Oxford University. Designed, conducted and analysed independently of the grant source (Merck & Co). No honoraria or consultancy fees accepted.





Men and women Aged 50-80 years Prior history of: myocardial infarction; ischaemic stroke or TIA; peripheral arterial disease; or diabetes with other CHD No contra-indication to study treatments No significant liver, kidney or muscle disease





#### HPS2-THRIVE: Active pre-randomization run-in





#### Characteristics of randomized participants

% or mean (SD)	ERN/LRPT (12,838)	Placebo (12,835)	All
Men	83%	83%	21,229 (83%)
Age (years)	64.9	64.9	64.9 (7.5)
Prior disease			
Coronary	78%	78%	20,137 (78%)
Cerebrovascular	32%	32%	8170 (32%)
Peripheral arterial	13%	12%	3214 (13%)
Diabetes	32%	32%	8299 (32%)





#### Baseline LIPIDS on statin-based therapy

	Mean (SD) baseline	
	mg/dL	mmol/L
Total cholesterol	128 (22)	3.32 (0.57)
Direct-LDL	63 (17)	1.64 (0.44)
HDL	44 (11)	1.14 (0.29)
Triglycerides*	125 (74)	1.43 (0.84)



\*64% fasted for >8 hours



#### Reasons for stopping study treatment

	ERN/LRPT (12,838)	Placebo (12,835)	Excess
Any medical	16.4%	7.9%	8.5%
Skin	5.4%	1.2%	4.2%
Gastrointestinal	3.9%	1.7%	2.1%
Musculoskeletal	1.8%	1.0%	0.8%
<b>Diabetes-related</b>	0.9%	0.4%	0.5%
Liver	0.4%	0.3%	0.1%
Other	4.1%	3.3%	0.8%
Any non-medical	8.9%	8.7%	0.3%
Any reason	25.4%	16.6%	8.7%



78% average compliance with active ERN/LRPT



# Effect of ERN/LRPT on SERIOUS adverse events (median follow-up 3.9 years)



#### Effect of ERN/LRPT on glucose related SAEs

Serious adverse event	ERN/LRPT	Placebo	Risk ratio (95% CI)
Participants with diabetes at rand	domization (n	= 8299)	
Minor hyperglycaemic problem	8.7%	5.8%	1.55 (1.32-1.82)
Major hyperglycaemic problem	1.0%	0.3%	3.09 (1.81-5.27)
Hypoglycaemia	1.1%	0.7%	1.50 (0.96-2.35)
Other diabetic complication	1.1%	1.2%	0.93 (0.62-1.40)
Any diabetic complication	460 (11.1%)	311 (7.5%)	1.55 (1.34-1.78)

#### Participants without diabetes at randomization (n= 17,374)

New-onset diabetes mellitus	792	632	1.27 (1.14-1.41)
	(9.1%)	(7.3%)	





#### Effect of ERN/LRPT on GI, muscle and skin SAEs

Serious Adverse Event	ERN/LRPT (12,838)	Placebo (12,835)	Risk ratio (95% CI)
Gastrointestinal			
GI bleeding	0.8%	0.6%	1.53 (1.14-2.05)
Peptic ulcer/upper GI	1.9%	1.4%	1.37 (1.13-1.65)
Lower GI	0.9%	0.7%	1.39 (1.06-1.83)
Other GI	1.0%	1.0%	0.99 (0.77-1.27)
Any gastrointestinal SAE	620 (4.8%)	491 (3.8%)	1.28 (1.13-1.44)
Musculoskeletal			
Myopathy	0.6%	0.1%	4.43 (2.62-7.50)
Gout	0.3%	0.2%	1.91 (1.16-3.15)
Other	2.9%	2.7%	1.08 (0.93-1.25)
Any musculoskeletal SAE	481 (3.7%)	385 (3.0%)	1.26 (1.10-1.44)
Skin	. ,		
Rash	0.4%	0.3%	1.63 (1.07-2.48)
Ulcer	0.2%	0.1%	1.61 (0.82-3.14)
Other	0.1%	0.0%	2.59 (1.05-6.37)
Any skin SAE	86 (0.7%)	51 (0.4%)	1.67 (1.20-2.34)

INIVERSITY O



#### Effect of ERN/LRPT on infection and bleeding

Serious Adverse Event	ERN/LRPT (12,838)	Placebo (12,835)	Risk ratio (95% CI)
Infection			
Lower respiratory	4.3%	3.7%	1.17 (1.03-1.32)
Urinary tract	0.9%	0.8%	1.07 (0.82-1.39)
Abdominal/gastrointestinal	0.6%	0.5%	1.26 (0.91-1.75)
Skin	0.5%	0.3%	1.66 (1.14-2.43)
Other	2.4%	1.7%	1.38 (1.16-1.63)
Any infection SAE	1031 (8.0%)	853 (6.6%)	1.22 (1.12-1.34)
Bleeding			
Gastrointestinal	0.8%	0.6%	1.53 (1.14-2.05)
Intracranial	1.1%	0.9%	1.17 (0.92-1.50)
Other	0.6%	0.4%	1.66 (1.18-2.34)
Any bleeding SAE	326 (2.5%)	238 (1.9%)	1.38 (1.17-1.62)





#### Prespecified efficacy outcomes

**Primary outcome:** MAJOR VASCULAR EVENTS (MVE) Defined as the first occurrence of either:

- MAJOR CORONARY EVENT = Non-fatal MI or coronary death;
- STROKE = Any non-fatal or fatal stroke (including subarachnoid haemorrhage); or
- REVASCULARIZATION = Coronary or non-coronary artery surgery or angioplasty (including amputation)

#### Secondary outcomes:

- Separate components of the primary outcome
- MVE in patients with or without coronary heart disease, cerebrovascular disease, peripheral artery disease and diabetes
- Mortality, overall and by specific causes of death





#### Effects of ER niacin/laropiprant on lipids

Year of FU	LDL-C (mg/dL)	HDL-C (mg/dL)	Triglycerides (mg/dL)
1	-12	6	-35
4	-7	6	-31
STUDY AVERAGE	-10	6	-33
(mmol/L)	(-0.25)	(0.16)	-0.37

"Based on previous observational studies and randomized trials, it was anticipated such lipid differences might translate into a 10-15% reduction in vascular events" Eur Heart Journal 2013





## Statistical power after about 4 years

#### Based on estimated 3200 MVEs during median follow-up of 4 years

Proportional	Statistical power at 2p:		
reduction in risk	<0.05	<0.01	
8%	67%	43%	
9%	78%	56%	
10%	86%	68%	
12%	96%	87%	





#### Effect of ERN/LRPT on MAJOR VASCULAR EVENTS



#### Effect of ERN/LRPT on MAJOR VASCULAR EVENTS





#### MVE by age, sex, region and statin-based therapy



#### Lipid differences (mg/dL) by age, sex, region and statin-based therapy

	Patients	LDL-C	HDL-C
Age (years)			
<65	12,932	-10	5
≥65 <70	5624	-11	7
≥70	7117	-8	7
Sex			
Male	21,229	-10	6
Female	4444	-8	7
Region			
Europe	14,741	-12	7
China	10,932	-7	5
Statin-based therapy			
Simvastatin 40mg	13,542	-8	6
Ezetimibe/simvastatin	, 12,131	-12	7
All	25,673	-10	6





#### MAJOR VASCULAR EVENTS by prior disease



#### Lipid differences (mg/dL) by prior disease

	Patients	LDL-C	HDL-C
Coronary heart disease			
Yes	20,137	-10	6
No	5536	-10	7
Cerebrovascular disease			
Yes	8170	-9	6
No	17,503	-10	7
Peripheral arterial diseas	se		
Yes	3214	-11	7
No	22,459	-9	6
Diabetes mellitus			
Yes	8299	-8	7
No	17,374	-10	6
All	25,673	-10	6





#### MAJOR VASCULAR EVENTS by baseline lipids





#### Lipid differences (mg/dL) by baseline lipids

mg/dL (mmol/L)	Patients	LDL-C	HDL-C
HDL cholesterol			
<35 (0.9)	4900	-7	5
≥35 <43	8135	-9	6
≥43 (1.1)	12,638	-11	7
LDL cholesterol			
<58 (1.5)	9860	-7	6
≥58 <77	11,054	-10	6
≥77 (2.0)	4759	-15	7
Triglycerides			
<89 (1.0)	8297	-9	6
≥89 <151	10,801	-10	6
≥151 (1.7)	6575	-10	6
All	25,673	-10	6





#### Effect of ERN/LRPT on CAUSE-SPECIFIC MORTALITY



## HPS2-THRIVE: SUMMARY

- Significant excesses of serious adverse events (SAEs) due to known and unrecognised side-effects of niacin. Over 4 years, ER niacin/laropiprant caused SAEs in ~30 patients per 1000
- No significant benefit of ER niacin/laropiprant on the primary outcome of major vascular events when added to effective statin-based LDL-lowering therapy
- No clear evidence of differences in efficacy or safety in different types of patient (except for an excess of statinrelated myopathy in Chinese patients)
- Findings are consistent with previous niacin trials. The role of ER niacin for the treatment and prevention of cardiovascular disease needs to be reconsidered





# European Medicine Agency announces review of niacin based on HPS2-THRIVE

"....assess the impact of the new data on the benefit-risk balance of these medicines, and will issue an opinion on whether the marketing authorisation should be maintained, varied, suspended or withdrawn across the EU."

#### March 2013







www.ctsu.ox.ac.uk/thrive

#### Back up slides

#### Effect of ERN/LRPT on SITE SPECIFIC CANCER INCIDENCE







# MAJOR VASCULAR EVENTS by low HDL/high triglycerides and prior statin use



#### MAJOR VASCULAR EVENTS by baseline lipids

