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

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HPS2-THRIVE: Eligibility

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

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HPS2-THRIVE: Active pre-randomization run-in

Screened (51,698)

High cardiovascular risk patients screened in 245 sites within 6 countries

LDL lowering phase (36,059)

Standardise background LDL-lowering therapy with simvastatin 40 mg (+/- ezetimibe) daily (to total cholesterol target of 135 mg/dL)

Active ER niacin plus laropiprant (38,369)

Test compliance with ER niacin 2 grams plus laropiprant 40 mg (ERN/LRPT) daily for 1 month

Randomization (25,673)

ER niacin 2g plus laropiprant 40 mg daily vs. matching placebo tablets

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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%)

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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

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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%
Diabetes-related	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

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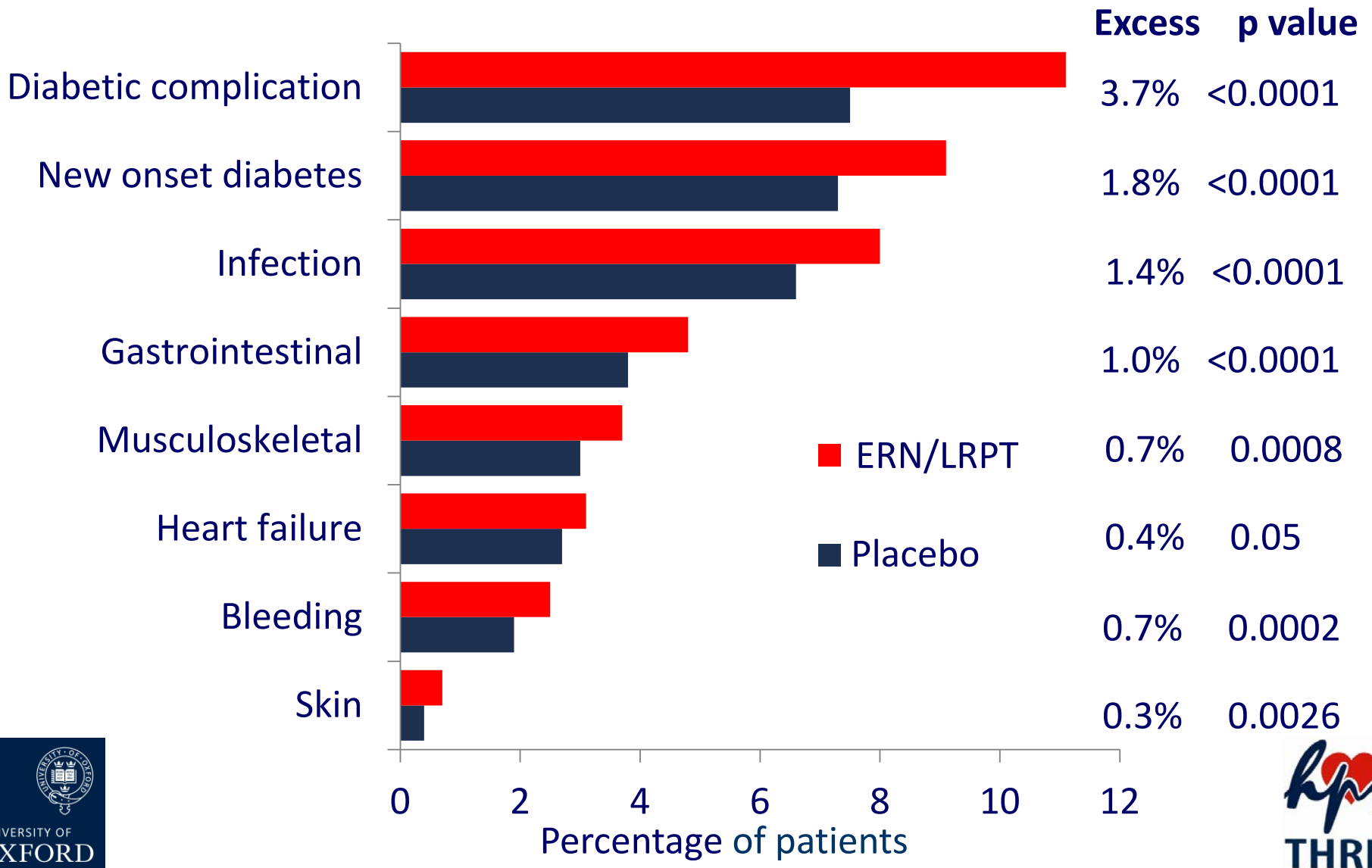
Effect of ERN/LRPT on SERIOUS adverse events (median follow-up 3.9 years)



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Effect of ERN/LRPT on glucose related SAEs

Serious adverse event	ERN/LRPT	Placebo	Risk ratio (95% CI)
Participants with diabetes at randomization (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 (9.1%)**	**632 (7.3%)**	**1.27 (1.14-1.41)**

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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)**

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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)**

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

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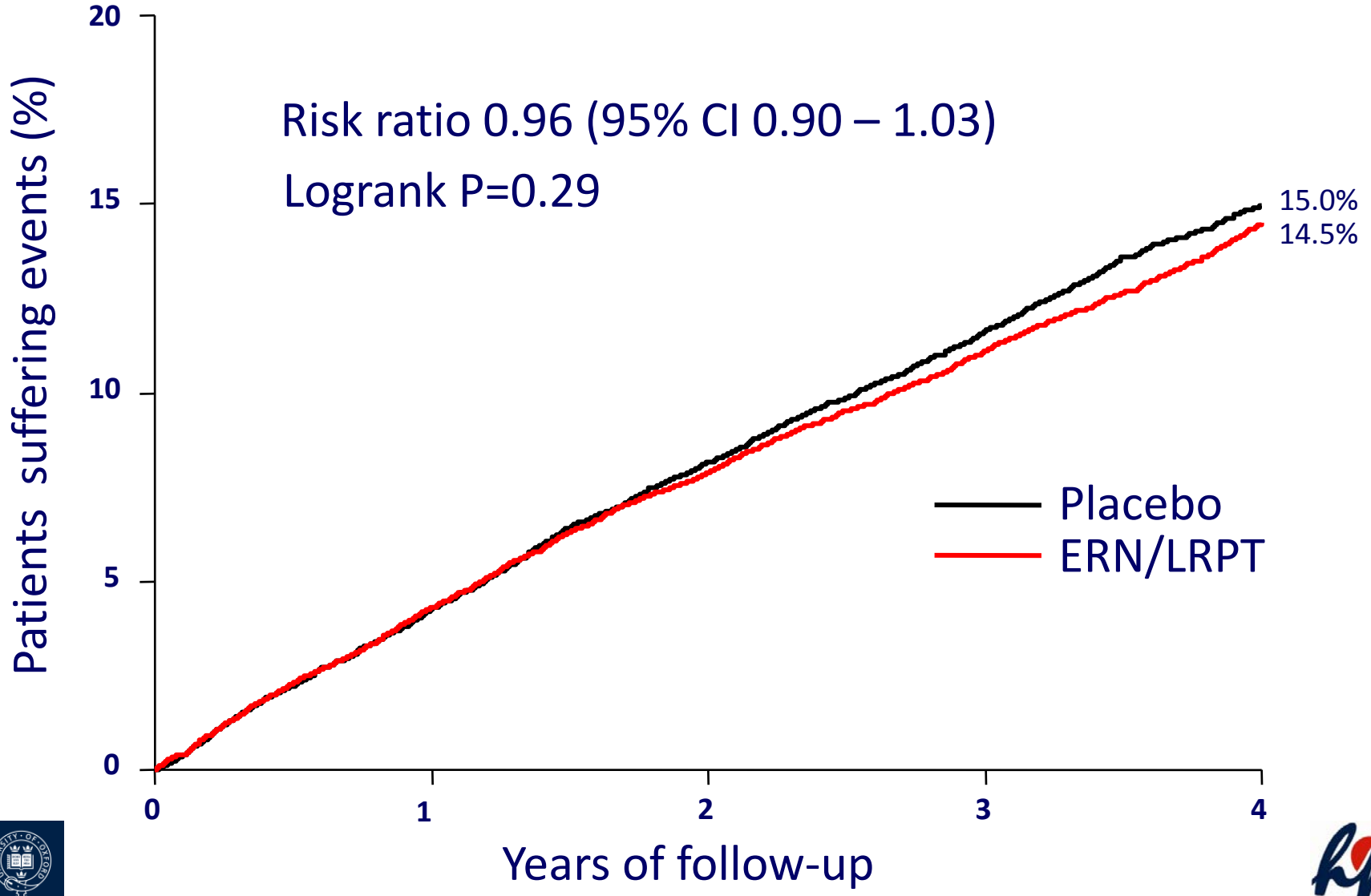
Effect of ERN/LRPT on MAJOR VASCULAR EVENTS



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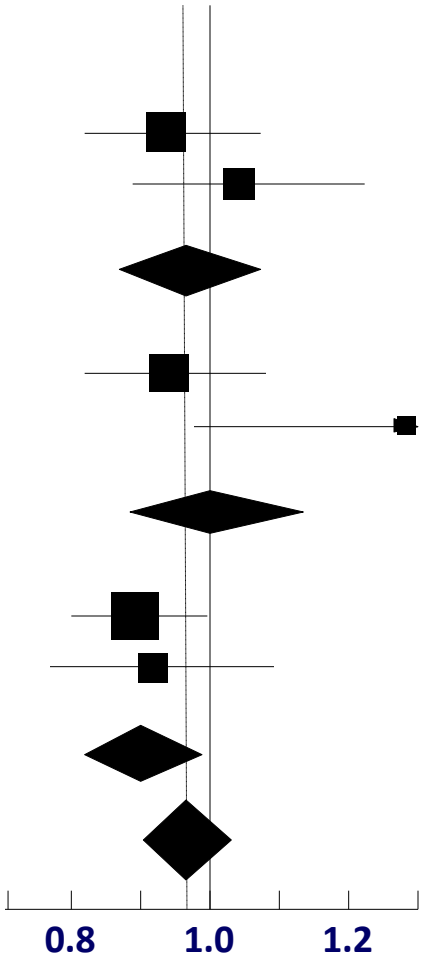
Effect of ERN/LRPT on MAJOR VASCULAR EVENTS

Event	Randomized allocation ERN/LRPT (12838)	Placebo (12835)	Risk ratio & 95% CI	p
Non-fatal MI	402 (3.1%)	431 (3.4%)	0.93 (0.82-1.07)	0.33
Coronary death	302 (2.4%)	291 (2.3%)	1.04 (0.89-1.22)	0.63
Major coronary event	**668 (5.2%)**	**694 (5.4%)**	**0.96 (0.87-1.07)**	**0.51**
Ischaemic stroke	389 (3.0%)	415 (3.2%)	0.94 (0.82-1.08)	0.37
Haemorrhagic stroke	114 (0.9%)	89 (0.7%)	1.28 (0.97-1.69)	0.08
Any stroke	**498 (3.9%)**	**499 (3.9%)**	**1.00 (0.88-1.13)**	**0.56**
Coronary revasc	591 (4.6%)	664 (5.2%)	0.89 (0.80-0.99)	0.04
Non-coronary revasc	236 (1.8%)	258 (2.0%)	0.92 (0.77-1.09)	0.33
Any revascularization	**807 (6.3%)**	**897 (7.0%)**	**0.90 (0.82-0.99)**	**0.03**
Major vascular event	**1696 (13.2%)**	**1758 (13.7%)**	**0.96 (0.90-1.03)**	**0.29**



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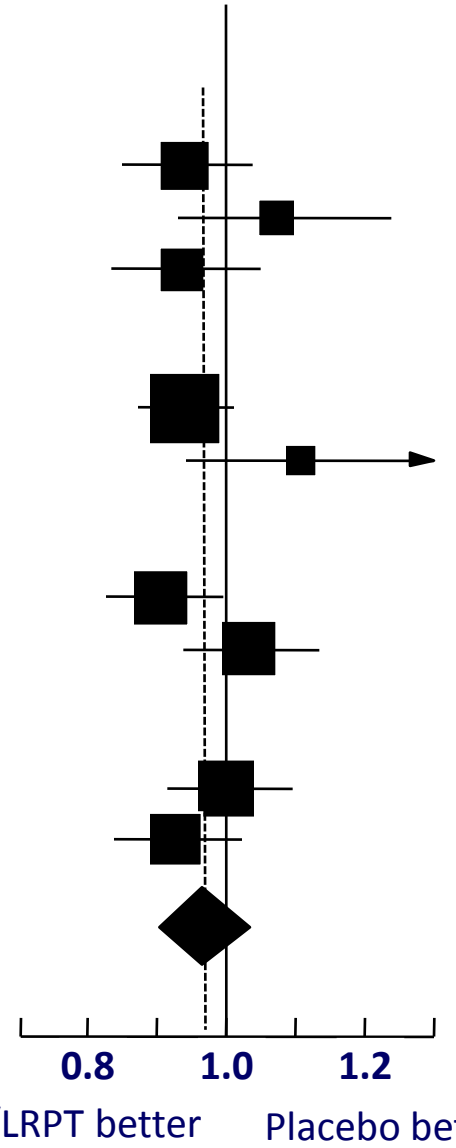
MVE by age, sex, region and statin-based therapy

	Randomized allocation ERN/LRPT (12,838)	Placebo (12,835)	Risk ratio & 95% CI	Het or trend χ^2 (uncorrected p value)
Age (years)				
< 65	740 (11.4%)	786 (12.2%)		0.00 (p=0.98)
≥ 65 <70	392 (13.9%)	367 (13.1%)		
≥ 70	564 (15.9%)	605 (17.0%)		
Sex				
Male	1397 (13.2%)	1485 (14.0%)		3.21 (p=0.07)
Female	299 (13.4%)	273 (12.3%)		
Region				
Europe	832 (11.3%)	913 (12.4%)		3.61 (p=0.06)
China	864 (15.8%)	845 (15.5%)		
Statin-based therapy				
Simvastatin 40mg	945 (14.0%)	949 (14.0%)		1.28 (p=0.26)
Ezetimibe/simvastatin	751 (12.4%)	809 (13.3%)		
All	**1696 (13.2%)**	**1758 (13.7%)**		**3.5% SE 3.3 reduction**



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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**

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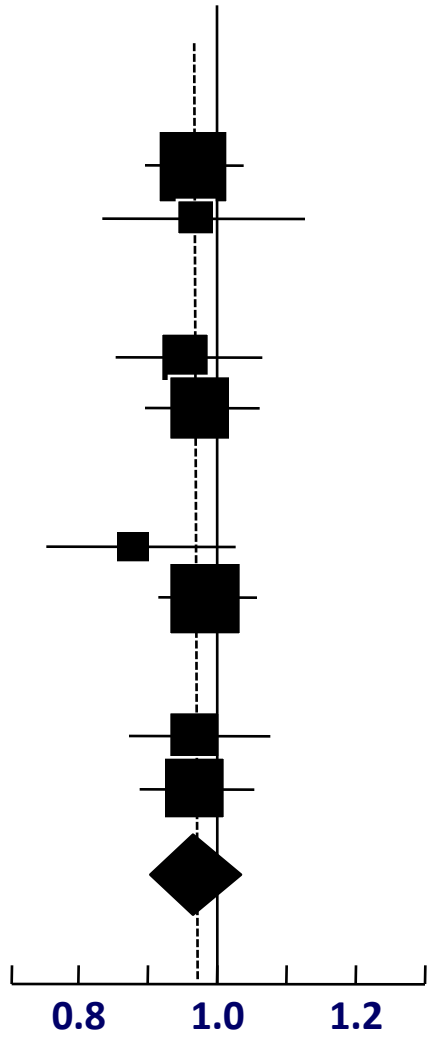
MAJOR VASCULAR EVENTS by prior disease

	Randomized allocation ERN/LRPT (12,838)	Randomized allocation Placebo (12,835)	Risk ratio & 95% CI	Het or trend χ^2 (uncorrected p value)
Coronary heart disease				
Yes	1361 (13.5%)	1413 (14.0%)		0.00 (p=0.96)
No	335 (12.1%)	345 (12.5%)		
Cerebrovascular disease				
Yes	616 (15.2%)	656 (16.0%)		0.10 (p=0.75)
No	1080 (12.3%)	1102 (12.6%)		
Peripheral arterial disease				
Yes	302 (18.6%)	332 (20.9%)		1.66 (p=0.20)
No	1394 (12.4%)	1426 (12.7%)		
Diabetes mellitus				
Yes	678 (16.4%)	708 (17.0%)		0.00 (p=0.98)
No	1018 (11.7%)	1050 (12.1%)		
All	**1696 (13.2%)**	**1758 (13.7%)**		**3.5% SE 3.3 reduction**



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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 disease			
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**

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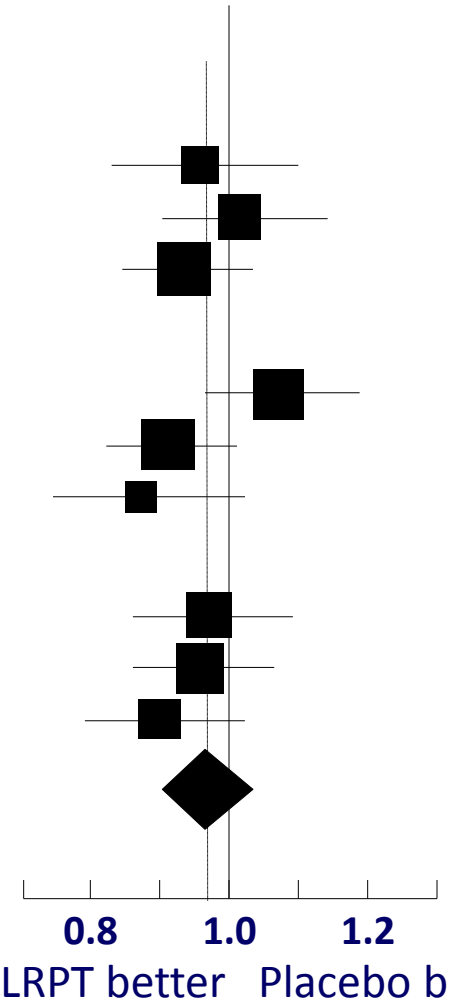
MAJOR VASCULAR EVENTS by baseline lipids

mg/dL (mmol/L)	Randomized allocation ERN/LRPT (12838)	Placebo (12835)	Risk ratio & 95% CI	Het or trend X^2 (uncorrected p value)
HDL cholesterol				
<35 (0.9)	388 (15.8%)	399 (16.3%)		0.20 (p=0.66)
≥35 <43	560 (13.7%)	546 (13.5%)		
≥43 (1.1)	748 (11.9%)	813 (12.8%)		
LDL cholesterol				
<58 (1.5)	724 (14.7%)	679 (13.8%)		5.91 (p=0.02)
≥58 <77	685 (12.4%)	761 (13.7%)		
≥77 (2.0)	287 (12.0%)	318 (13.5%)		
Triglycerides				
<89 (1.0)	541 (13.2%)	563 (13.4%)		0.66 (p=0.42)
≥89 <151	694 (12.8%)	712 (13.2%)		
≥151 (1.7)	461 (13.9%)	483 (14.8%)		
All	**1696 (13.2%)**	**1758 (13.7%)**		**3.5% SE 3.3 reduction**



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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**

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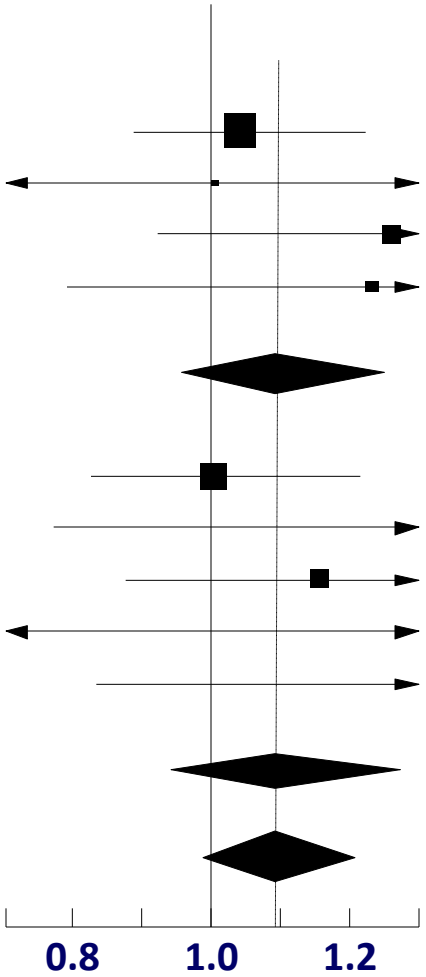
Effect of ERN/LRPT on CAUSE-SPECIFIC MORTALITY

	Randomized allocation ERN/LRPT (12838)	Placebo (12835)	Risk ratio & 95% CI	p
Coronary	302 (2.4%)	291 (2.3%)		
Other cardiac	15 (0.1%)	15 (0.1%)		
Stroke	88 (0.7%)	70 (0.5%)		
Other vascular	43 (0.3%)	35 (0.3%)		
Vascular	**448 (3.5%)**	**411 (3.2%)**	**1.09 (0.96-1.25)**	**0.19**
Neoplastic	206 (1.6%)	206 (1.6%)		
Hepatic	3 (0.0%)	0 (0.0%)		
Other medical	106 (0.8%)	92 (0.7%)		
Non-medical	16 (0.1%)	12 (0.1%)		
Unknown	19 (0.1%)	11 (0.1%)		
Non-vascular	**350 (2.7%)**	**321 (2.5%)**	**1.09 (0.94-1.27)**	**0.25**
Any cause	**798 (6.2%)**	**732 (5.7%)**	**1.09 (0.99-1.21)**	**0.08**



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HPS2-THRIVE: SUMMARY

- No significant benefit of ER niacin/laropiprant on the primary outcome of major vascular events when added to effective statin-based LDL-lowering therapy
- 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 clear evidence of differences in efficacy or safety in different types of patient (except for an excess of statin-related 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

www.ctsu.ox.ac.uk/thrive