Supplementary material to:

Trials in "true" dyslipidemic patients are urged to reconsider comprehensive lipid management as a means to reduce residual cardiovascular risk

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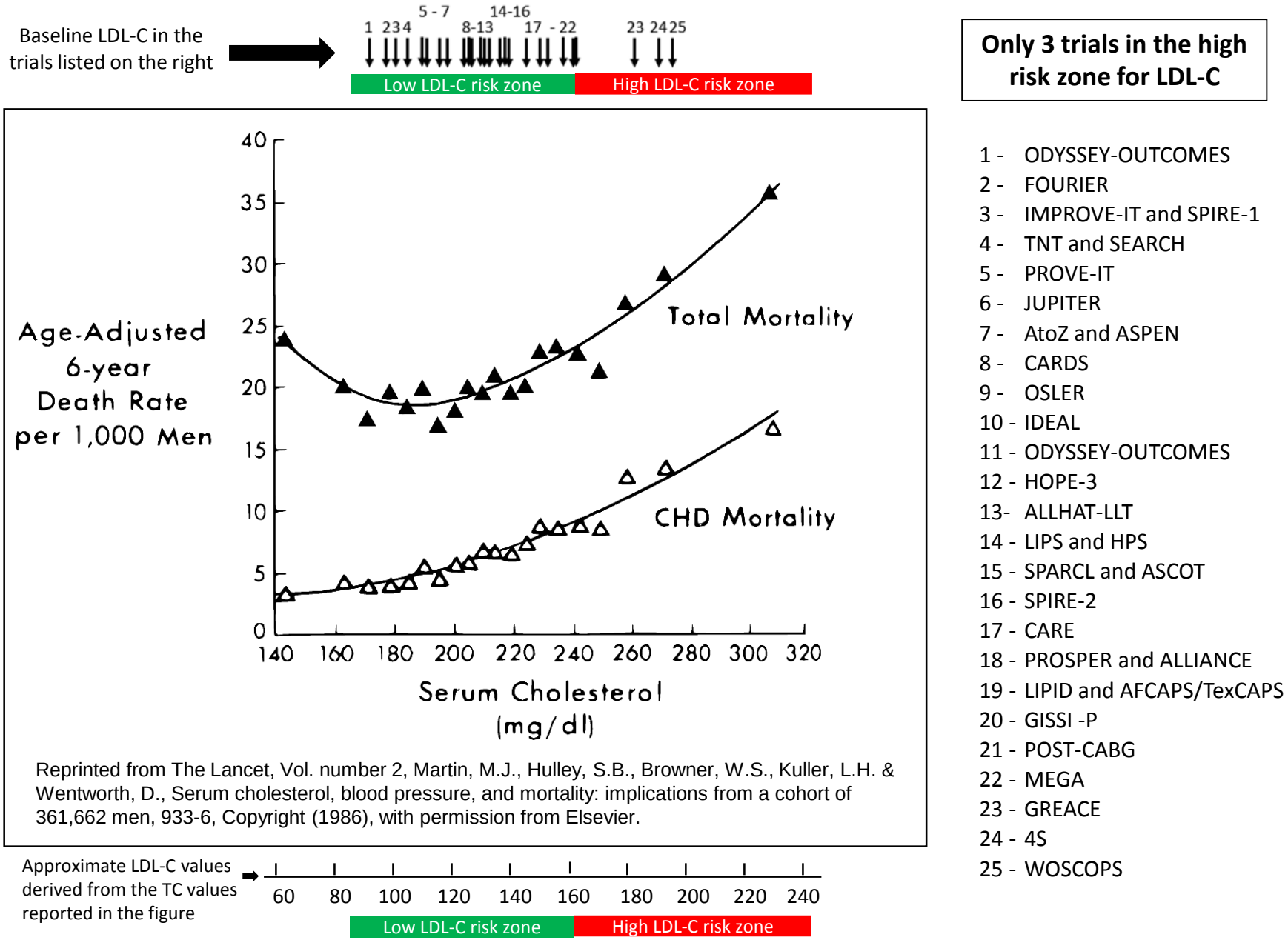
Figure S1. Mismatch between baseline LDL-C levels at trial entry and range of lipid-related high cardiovascular risk (red zone)



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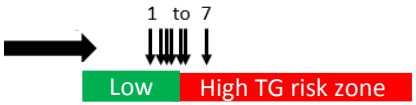
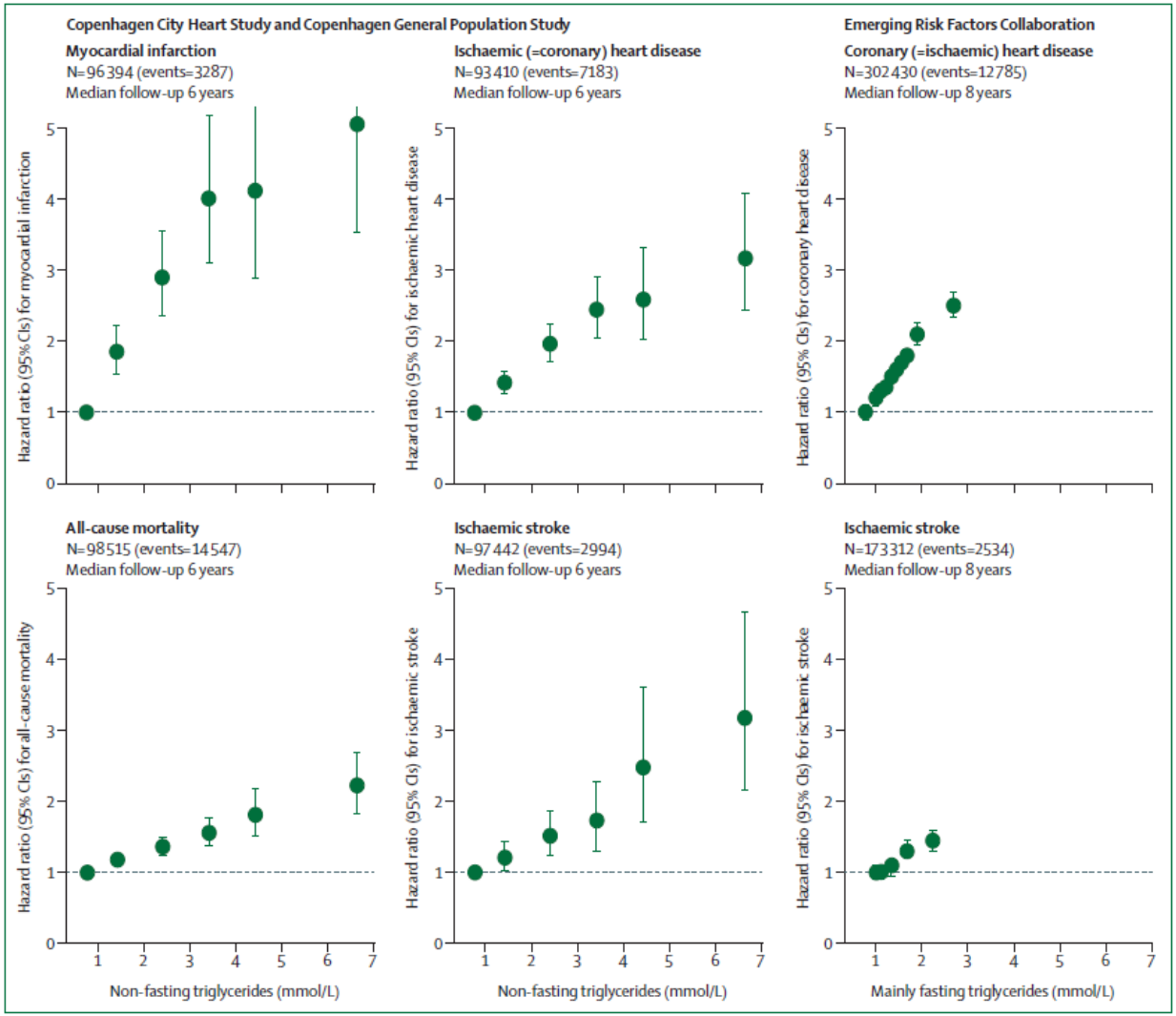
Only 3 trials in the high risk zone for LDL-C

1 - ODYSSEY-OUTCOMES
2 - FOURIER
3 - IMPROVE-IT and SPIRE-1
4 - TNT and SEARCH
5 - PROVE-IT
6 - JUPITER
7 - AtoZ and ASPEN
8 - CARDS
9 - OSLER
10 - IDEAL
11 - ODYSSEY-OUTCOMES
12 - HOPE-3
13- ALLHAT-LLT
14 - LIPS and HPS
15 - SPARCL and ASCOT
16 - SPIRE-2
17 - CARE
18 - PROSPER and ALLIANCE
19 - LIPID and AFCAPS/TexCAPS
20 - GISSI -P
21 - POST-CABG
22 - MEGA
23 - GREACE
24 - 4S
25 - WOSCOPS

Figure S2. Mismatch between baseline triglyceride levels at trial entry and range of lipid-related high cardiovascular risk (red zone)

Baseline TG in the trials listed on the right





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All trials in the normal/borderline risk zone for TG

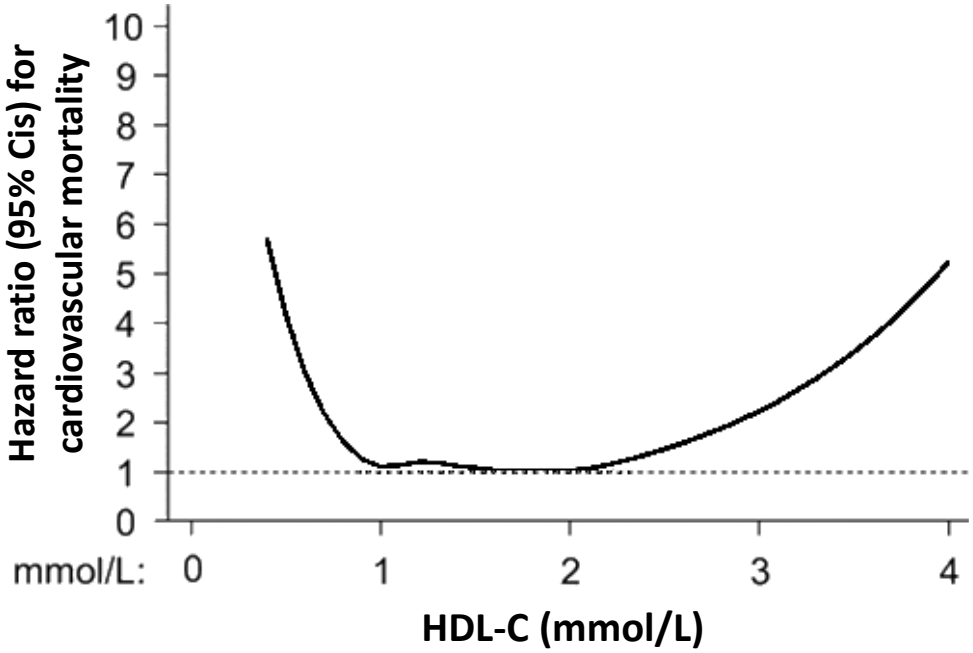
The mismatch between baseline TG in the trials and TG-related risk is shown in reference to ischemic (coronary) heart disease outcomes (top panel, middle graph). The same concept may be applied to other cardiovascular outcomes.

-1 BIP
-2 VA-HIT
-3 FIELD
-4 HHS
-5 LEADER
-6 ACCORD
-7 DAIS

Figure S3. Mismatch between baseline HDL-C levels at trial entry and range of lipid-related high cardiovascular risk (red zone)

Baseline HDL-C in the trials listed on the right

Only 1 trial in the borderline risk zone for HDL-C



Adapted from Madsen, C.M., Varbo, A. & Nordestgaard, B.G. Extreme high high-density lipoprotein cholesterol is paradoxically associated with high mortality in men and women: two prospective cohort studies. *Eur Heart J* 2017, 38, 2478-86, by permission of Oxford University Press

- 1 AIM-HIGH
- 2 REVEAL
- 3 DAL-OUTCOMES
- 4 HPS2-THRIVE
- 5 ACCELERATE
- 6 ILLUMINATE

Table S1. Data of cardiovascular LDL-C trials included in Figure 2 (meta-regression analysis) of the main manuscript.

LDL TRIAL	MEAN/MEDIAN Baseline LDL-C (intervention group)	Test treatment	Control treatment	Prevention	n= experimental group	n= control group	Achieved LDL-C mg/dl (experimental group)	Achieved LDL-C mg/dl (control group)	Between-group absolute difference achieved LDL-C (mg/dl)	Major Vascular Events (exp group)	Major Vascular Events (control group)	Relative Risk of major vascular events	Selected composite endpoint*
WOSCOPS	192	Prava 40	Placebo	Primary	3302	3293	142	192	50	174	248	0.69 (0.57, 0.83)	1,6
4S	188	Simva 20-40	Placebo	Secondary	2221	2223	123	191	68	431	622	0.66 (0.59, 0.74)	1,2,6
GREACE	180	Atorva 10–80	Usual care	Secondary	800	800	97	169	72	41	89	0.46 (0.32, 0.66)	1,6
MEGA	157	Prava 10–20	Usual care	Primary	3866	3966	127	149	22	98	144	0.70 (0.54, 0.90)	1,3,4,5,6
POST-CABG	156	Lova 40-80	Lova 2,5-5	Secondary	676	675	93	136	43	85	103	0.82 (0.63, 1.07)	1,4,5,8
GISSI -P	152	Prava 20	No treatment	Secondary	2138	2133	130	146	17	120	136	0.90 (0.71, 1.15)	1,5,8
LIPID	150	Prava 40	Placebo	Secondary	4512	4502	113	150	38	557	715	0.76 (0.68, 0.85)	1,6
AFCAPS/TEXCAPS	150	Lova 20–40	Placebo	Primary	3304	3301	115	158	43	116	183	0.63 (0.50, 0.79)	1,3,6
PROSPER	147	Prava 40	Placebo	Both	2891	2913	107	147	40	408	473	0.85 (0.74, 0.97)	1,5,6
ALLIANCE	147	Atorva 10-80	Usual care	Secondary	1217	1225	95	110	15	289	333	0.83 (0.71, 0.97)	1,2,3,4,6
CARE	139	Prava 40	Placebo	Secondary	2081	2078	98	136	38	212	274	0.76 (0.64, 0.91)	1,6
SPIRE-2	134	Bococizumab	Placebo	Both	5312	5309	80	137	58	179	224	0.79 (0.65, 0.97)	1,3,5,7
SPARCL	133	Atorva 80	Placebo	Secondary	2365	2366	73	129	56	334	407	0.80 (0.69, 0.92)	1,2,5,6
ASCOT-LLA	133	Atorva 10	Placebo	Primary	5168	5137	90	127	37	100	154	0.64 (0.50, 0.83)	1,6
LIPS	131	Fluva 80	Placebo	Secondary	844	833	97	138	41	181	222	0.78 (0.64, 0.95)	1,4,6
HPS	131	Simva 40	Placebo	Both	10269	10267	89	128	39	2033	2585	0.76 (0.72, 0.81)	1,4,5,6
ALLHAT-LLT	129	Prava 40	Usual care	Both	5170	5185	111	135	24	380	421	0.91 (0.79, 1.04)	1,6
HOPE-3	128	Rosuva 10	Placebo	Primary	6361	6344	96	125	30	235	304	0.76 (0.64, 0.91)	1,5,7
ODYSSEY LONG TERM	123	Alirocumab	Placebo	Both	1553	788	48	119	71	27	26	0.52 (0.31, 0.90)	1,2,3,5
IDEAL	122	Atorva 40–80	Simva 20-40	Secondary	4439	4449	82	104	22	533	608	0.87 (0.78, 0.98)	1,2,5,6
OSLER	120	Evolocumab	Standard therapy	Both	2976	1489	48	120	72	28	30	0.47 (0.28, 0.78)	1,3,4,5,8,9,10
CARDS	118	Atorva 10	Placebo	Primary	1428	1410	82	121	39	83	127	0.63 (0.48, 0.83)	1,3,4,5,6
ASPEN	113	Atorva 10	Placebo	Both	1211	1199	79	113	34	166	180	0.90 (0.73, 1.12)	1,2,3,4,5,7
AtoZ	112	Simva 40-80	Simva 20	Secondary	2265	2232	66	81	15	309	343	0.89 (0.76, 1.04)	1,3,5,7

JUPITER	108	Rosuva 20	Placebo	Primary	8901	8901	55	109	54	142	251	0.56 (0.46, 0.69)	1,3,4,5,7
PROVE-IT	106	Atorva 80	Prava 40	Secondary	2099	2063	62	95	33	464	537	0.84 (0.74, 0.95)	1,3,4,5,8
TNT	97	Atorva 80	Atorva 10	Secondary	4995	5006	77	101	24	434	548	0.78 (0.69, 0.89)	1,2,5,6
SEARCH	97	Simva 80	Simva 20	Secondary	6031	6033	83	97	14	1477	1553	0.94 (0.88, 1.01)	1,4,5,6
SPIRE-1	94	Bococizumab	Placebo	Both	8408	8409	52	100	48	173	173	0.99 (0.80, 1.22)	1,3,5,7
IMPROVE-IT	94	Ezetimibe 10	Placebo	Secondary	9067	9077	54	70	16	2572	2742	0.94 (0.89, 0.99)	1,2,3,5,7
FOURIER	92	Evolocumab	Placebo	Secondary	13784	13780	30	90	60	1344	1563	0.85 (0.79, 0.92)	1,3,4,5,7
ODYSSEY-OUTCOMES	87	Alirocumab	Placebo	Secondary	9462	9462	47	97	50	903	1052	0.85 (0.78, 0.93)	1,3,5,6

The cardiovascular LDL-C trials are sorted according to the mean baseline LDL-C level in the intervention group (from the highest to the lowest). Doses of statins and ezetimibe are expressed in mg/day. For statin trials, the outcome “major vascular events” used in this meta-regression were the combined outcomes selected in the statin meta-analysis reported by Silverman et al (reference 19) whereas for IMPROVE-IT and for trials with pcsk-9 inhibitors, “major vascular events” were the combined primary outcomes of each trial. The last column lists the individual components of the combined outcome for each study, as follows: 1: myocardial infarction; 2: resuscitated cardiac arrest; 3: hospitalization for unstable angina; 4: coronary revascularization; 5: stroke; 6: coronary death; 7: cardiovascular death; 8: all cause mortality; 9: transit ischemic atack; 10: heart failure.