Reassessing the role of triglycerides in cardiovascular disease residual risk

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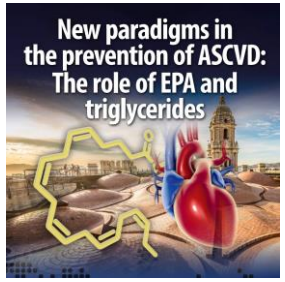
New paradigms in the prevention of ASCVD: The role of EPA and triglycerides



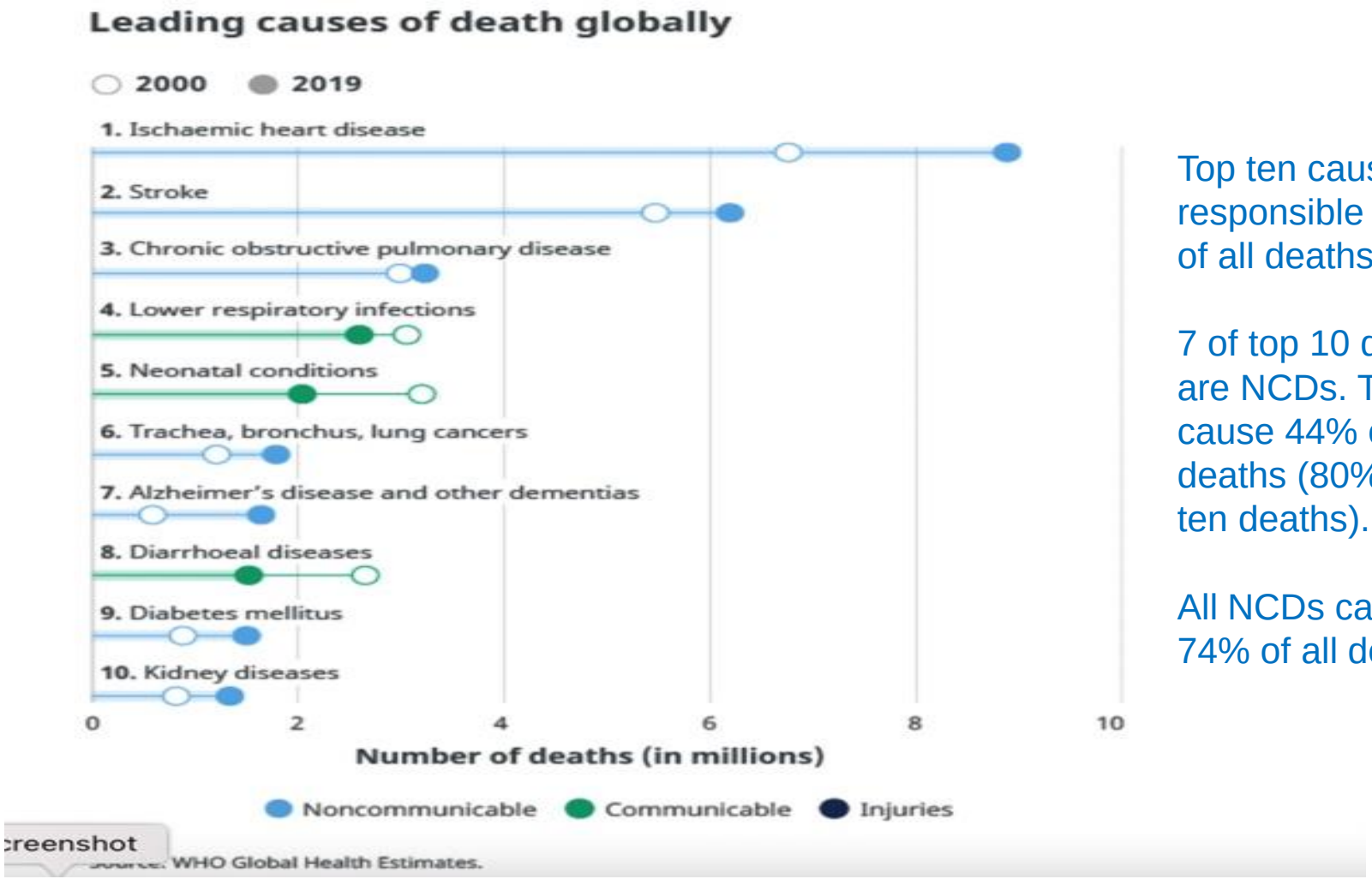
PHYSICIANS' ACADEMY FOR
PACE-CME
CARDIOVASCULAR EDUCATION

Presentation summary

- Global importance of CVD
- CVD main risk factors and role of lipids
- Residual risk in CVD prevention
- Evidence for the role of triglycerides in CVD residual risk

Global importance of CVD prevention

Global causes of death 2022



Top ten causes responsible for 55% of all deaths

7 of top 10 deaths are NCDs. These 7 cause 44% of all deaths (80% of top ten deaths).

All NCDs cause 74% of all deaths

https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death

Global leading causes of DALYs 1990-2019

E 50–74 years

Leading causes 1990	Percentage of DALYs 1990	Leading causes 2019	Percentage of DALYs 2019	Percentage change in number of DALYs, 1990–2019	Percentage change in age-standardised DALY rate, 1990–2019
1 Ischaemic heart disease	12·5 (11·6 to 13·4)	1 Ischaemic heart disease	11·8 (10·7 to 12·9)	46·1 (35·6 to 56·4)	−29·1 (−34·2 to −24·1)
2 Stroke	10·9 (10·0 to 11·8)	2 Stroke	9·3 (8·5 to 10·1)	31·5 (19·5 to 42·9)	−36·3 (−42·1 to −30·8)
3 COPD	6·5 (5·5 to 7·1)	3 Diabetes	5·1 (4·6 to 5·7)	156·1 (143·4 to 167·9)	24·5 (18·5 to 30·4)
4 Tuberculosis	4·0 (3·6 to 4·4)	4 COPD	4·7 (4·2 to 5·2)	12·0 (0·9 to 32·3)	−45·9 (−51·4 to −36·2)
5 Lung cancer	3·6 (3·3 to 3·9)	5 Lung cancer	3·9 (3·4 to 4·3)	64·3 (48·8 to 80·2)	−19·8 (−27·3 to −12·1)
6 Diabetes	3·1 (2·8 to 3·4)	6 Low back pain	3·1 (2·3 to 4·0)	72·1 (70·0 to 74·3)	−15·9 (−16·9 to −14·9)
7 Cirrhosis	2·8 (2·6 to 3·1)	7 Cirrhosis	2·7 (2·4 to 3·0)	44·6 (33·2 to 57·1)	−29·1 (−34·7 to −23·0)
8 Low back pain	2·8 (2·1 to 3·7)	8 Chronic kidney disease	2·3 (2·1 to 2·5)	130·2 (113·0 to 145·6)	12·1 (3·7 to 19·5)
9 Diarrhoeal diseases	2·6 (1·6 to 4·0)	9 Age-related hearing loss	2·2 (1·5 to 3·0)	100·8 (96·0 to 104·9)	−2·6 (−4·9 to −0·5)
10 Stomach cancer	2·4 (2·2 to 2·6)	10 Road injuries	2·1 (1·9 to 2·3)	72·9 (56·5 to 83·9)	−15·2 (−23·2 to −9·9)
11 Road injuries	1·9 (1·8 to 2·0)	11 Other musculoskeletal	1·9 (1·4 to 2·6)	172·0 (160·6 to 187·4)	33·6 (280 to 40·2)
12 Lower respiratory infections	1·8 (1·6 to 2·0)	12 Tuberculosis	1·9 (1·7 to 2·1)	−27·8 (−36·2 to −16·9)	−64·7 (−68·9 to −59·4)
13 Age-related hearing loss	1·7 (1·2 to 2·3)	13 Lower respiratory infections	1·8 (1·6 to 1·9)	49·8 (37·9 to 62·4)	−27·5 (−33·3 to −21·5)
14 Chronic kidney disease	1·6 (1·4 to 1·7)	14 Depressive disorders	1·7 (1·3 to 2·3)	107·3 (104·7 to 110·1)	1·5 (0·2 to 2·9)
15 Asthma	1·5 (1·2 to 1·9)	15 Colorectal cancer	1·7 (1·6 to 1·9)	95·1 (80v8 to 108·2)	−5·1 (−12·1 to 1·2)
16 Hypertensive heart disease	1·5 (1·2 to 1·7)	16 Falls	1·7 (1·5 to 2·0)	88·3 (76·5 to 100·0)	−8·4 (−14·1 to −2·6)
17 Falls	1·4 (1·3 to 1·6)	17 Stomach cancer	1·7 (1·5 to 1·9)	6·3 (−5·0 to 18·9)	−48·1 (−536 to −42·0)
18 Colorectal cancer	1·4 (1·3 to 1·5)	18 Osteoarthritis	1·5 (0·8 to 2·9)	113·6 (110·9 to 116·4)	4·1 (28 to 5·4)
19 Depressive disorders	1·3 (0·9 to 1·7)	19 Blindness and vision loss	1·4 (1·1 to 2·0)	88·8 (81·9 to 95·8)	−8·6 (−12·0 to −5·0)
20 Blindness and vision loss	1·2 (0·9 to 1·6)	20 Breast cancer	1·4 (1·3 to 1·5)	85·0 (69·9 to 99·4)	−9·5 (−16·9 to −2·5)
21 Liver cancer	1·2 (1·0 to 1·3)	21 Diarrhoeal diseases	1·4 (0·9 to 2·1)	−21·0 (−42·4 to 11·9)	−61·0 (−72·1 to −45·8)
22 Breast cancer	1·2 (1·1 to 1·2)	22 Hypertensive heart disease	1·3 (1·0 to 1·5)	36·7 (20·8 to 58·8)	−33·8 (−41·7 to −23·4)
23 Oesophageal cancer	1·1 (0·9 to 1·2)	23 Headache disorders	1·2 (0·4 to 2·5)	102·5 (88·7 to 108·2)	−1·2 (−7·4 to 2·3)
24 Osteoarthritis	1·1 (0·6 to 2·2)	24 Oral disorders	1·2 (0·8 to 1·8)	90·5 (86·0 to 94·7)	−7·4 (−9·6 to −5·1)
25 Self-harm	1·1 (1·0 to 1·2)	25 Neck pain	1·1 (0·7 to 1·7)	115·9 (110·5 to 122·2)	5·7 (3·0 to 8·5)
26 Other musculoskeletal	1·1 (0·7 to 1·5)	27 Oesophageal cancer	1·0 (0·9 to 1·1)	38·2 (18·9 to 71·9)	−32·1 (−41·9 to −16·1)
28 Oral disorders	1·0 (0·6 to 1·5)	28 Asthma	1·0 (0·8 to 1·1)	−1·3 (−14·3 to 11·2)	−51·8 (−58·3 to −46·0)
29 Headache disorders	0·9 (0·3 to 1·9)	29 Liver cancer	0·9 (0·8 to 1·0)	22·2 (5·2 to 44·0)	−39·9 (−48·5 to −29·5)
32 Neck pain	0·8 (0·5 to 1·2)	31 Self-harm	0·9 (0·8 to 1·0)	20·4 (11·3 to 33·7)	−41·0 (−45·5 to −34·5)

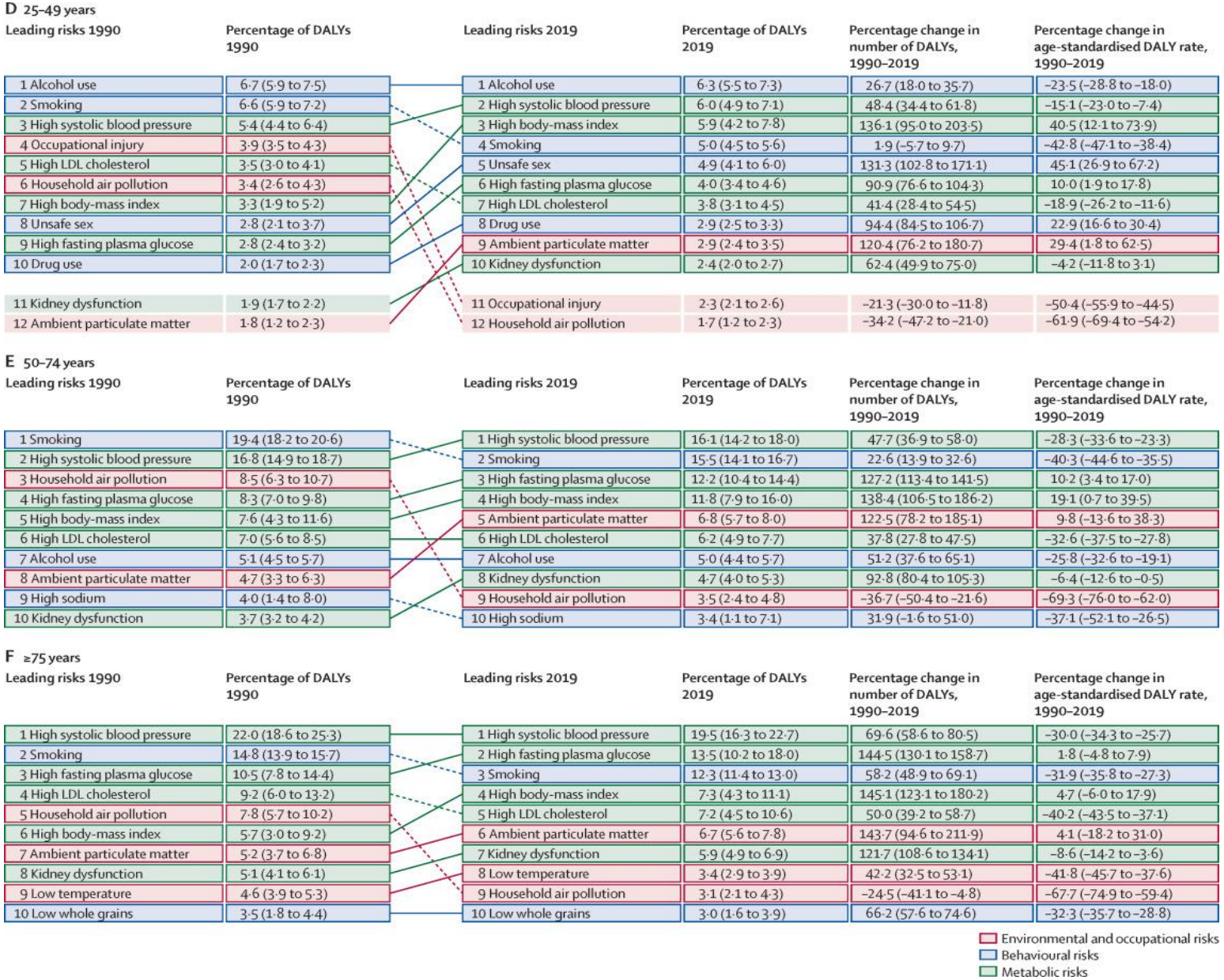
F 75 years and older

1 Ischaemic heart disease	18·6 (17·1 to 19·7)	1 Ischaemic heart disease	16·2 (14·6 to 17·6)	66·6 (57·7 to 74·2)	−32·4 (−35·8 to −29·4)
2 Stroke	15·5 (14·3 to 16·7)	2 Stroke	13·0 (11·7 to 14·0)	60·5 (48·7 to 72·5)	−33·4 (−38·3 to −28·5)
3 COPD	9·9 (8·6 to 10·7)	3 COPD	8·5 (7·5 to 9·2)	63·6 (49·1 to 86·1)	−31·0 (−37·1 to −21·9)
4 Alzheimer's disease	3·8 (1·7 to 8·6)	4 Alzheimer's disease	5·6 (2·6 to 12·2)	180·0 (168·0 to 194·7)	2·6 (−2·1 to 6·6)
5 Lower respiratory infections	3·3 (3·0 to 3·6)	5 Diabetes	4·0 (3·6 to 4·3)	190·7 (179·4 to 201·0)	23·1 (18·6 to 27·5)
6 Diarrhoeal diseases	3·1 (2·0 to 4·5)	6 Lower respiratory infections	3·3 (2·9 to 3·6)	87·4 (76·2 to 99·6)	−25·3 (−29·3 to −20·4)
7 Diabetes	2·6 (2·4 to 2·9)	7 Lung cancer	2·6 (2·3 to 2·8)	164·3 (143·6 to 183·8)	16·4 (7·4 to 24·9)
8 Hypertensive heart disease	2·3 (1·9 to 2·5)	8 Falls	2·6 (2·2 to 2·9)	166·4 (151·1 to 183·4)	6·4 (0·4 to 13·3)
9 Age-related hearing loss	2·0 (1·5 to 2·7)	9 Chronic kidney disease	2·5 (2·3 to 2·7)	196·0 (173·9 to 211·1)	21·6 (12·6 to 27·4)
10 Lung cancer	1·9 (1·8 to 2·0)	10 Age-related hearing loss	2·5 (1·9 to 3·3)	137·8 (132·0 to 143·9)	−2·2 (−4·3 to −0·2)
11 Falls	1·8 (1·6 to 2·1)	11 Hypertensive heart disease	2·4 (1·8 to 2·7)	106·0 (68·5 to 131·7)	−15·1 (−31·5 to −5·0)
12 Tuberculosis	1·8 (1·6 to 2·1)	12 Diarrhoeal diseases	1·9 (1·2 to 3·0)	15·1 (−16·8 to 65·3)	−51·0 (−64·9 to −30·4)
13 Low back pain	1·7 (1·2 to 2·3)	13 Low back pain	1·8 (1·3 to 2·4)	105·7 (100·2 to 111·4)	−12·5 (−13·8 to −11·3)
14 Chronic kidney disease	1·6 (1·5 to 1·8)	14 Colorectal cancer	1·7 (1·5 to 1·8)	126·9 (113·4 to 138·3)	−4·5 (−9·7 to 0·1)
15 Stomach cancer	1·6 (1·4 to 1·7)	15 Blindness and vision loss	1·7 (1·3 to 2·2)	124·7 (119·3 to 130·7)	−7·4 (−9·9 to −4·8)
16 Blindness and vision loss	1·4 (1·1 to 1·8)	16 Atrial fibrillation	1·3 (1·1 to 1·5)	148·6 (134·8 to 161·9)	−1·8 (−6·9 to 2·5)
17 Colorectal cancer	1·4 (1·3 to 1·5)	17 Stomach cancer	1·3 (1·1 to 1·4)	55·0 (43·8 to 66·6)	−32·9 (−37·5 to −28·0)
18 Asthma	1·2 (1·0 to 1·7)	18 Prostate cancer	1·1 (1·0 to 1·4)	117·0 (102·1 to 142·3)	−8·5 (−14·6 to 2·1)
19 Cirrhosis	1·2 (1·0 to 1·3)	19 Cirrhosis	1·1 (1·0 to 1·2)	82·3 (62·1 to 100·9)	−21·3 (−30·2 to −13·5)
20 Prostate cancer	1·0 (0·8 to 1·2)	20 Parkinson's disease	1·1 (1·0 to 1·2)	153·7 (138·7 to 166·6)	6·0 (0·0 to 11·1)
21 Atrial fibrillation	1·0 (0·8 to 1·2)	21 Osteoarthritis	1·1 (06 to 21)	139·5 (136·5 to 142·6)	0·8 (−0·4 to 2·1)
22 Osteoarthritis	0·9 (0·5 to 1·7)	22 Oral disorders	0·9 (0·6 to 1·3)	112·0 (106·4 to 117·6)	−10·9 (−12·9 to −8·8)
23 Oral disorders	0·8 (0·6 to 1·2)	23 Tuberculosis	0·9 (0·8 to 1·0)	−6·3 (−16·9 to 14·6)	−59·2 (−64·0 to −50·3)
24 Parkinson's disease	0·8 (0·8 to 0·9)	24 Asthma	0·8 (0·7 to 1·0)	25·2 (3·2 to 41·2)	−46·2 (−55·9 to −39·8)
25 Upper digestive diseases	0·8 (0·7 to 0·9)	25 Road injuries	0·8 (0·7 to 0·9)	110·0 (99·8 to 118·1)	−9·3 (−13·5 to −5·9)
26 Road injuries	0·7 (0·6 to 0·8)	32 Upper digestive diseases	0·6 (0·5 to 0·6)	34·0 (22·8 to 46·2)	−43·8 (−48·4 to −38·7)

Communicable, maternal, neonatal, and nutritional diseases
Non-communicable diseases
Injuries

BD 2019 Diseases and Injuries Collaborators. **Global burden of 369 diseases and injuries, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019.** *The Lancet*. 17 October 2020. doi:10.1016/S0140-6736(20)30925-9.

Global main risk factors for DALYs 1990-2019



D 25–49 years

Leading risks 1990	Percentage of DALYs 1990	Leading risks 2019	Percentage of DALYs 2019	Percentage change in number of DALYs, 1990–2019	Percentage change in age-standardised DALY rate, 1990–2019
1 Alcohol use	6·7 (5·9 to 7·5)	1 Alcohol use	6·3 (5·5 to 7·3)	26·7 (18·0 to 35·7)	−23·5 (−28·8 to −18·0)
2 Smoking	6·6 (5·9 to 7·2)	2 High systolic blood pressure	6·0 (4·9 to 7·1)	48·4 (34·4 to 61·8)	−15·1 (−23·0 to −7·4)
3 High systolic blood pressure	5·4 (4·4 to 6·4)	3 High body-mass index	5·9 (4·2 to 7·8)	136·1 (95·0 to 203·5)	40·5 (12·1 to 73·9)
4 Occupational injury	3·9 (3·5 to 4·3)	4 Smoking	5·0 (4·5 to 5·6)	1·9 (−5·7 to 9·7)	−42·8 (−47·1 to −38·4)
5 High LDL cholesterol	3·5 (3·0 to 4·1)	5 Unsafe sex	4·9 (4·1 to 6·0)	131·3 (102·8 to 171·1)	45·1 (26·9 to 67·2)
6 Household air pollution	3·4 (2·6 to 4·3)	6 High fasting plasma glucose	4·0 (3·4 to 4·6)	90·9 (76·6 to 104·3)	10·0 (1·9 to 17·8)
7 High body-mass index	3·3 (1·9 to 5·2)	7 High LDL cholesterol	3·8 (3·1 to 4·5)	41·4 (28·4 to 54·5)	−18·9 (−26·2 to −11·6)
8 Unsafe sex	2·8 (2·1 to 3·7)	8 Drug use	2·9 (2·5 to 3·3)	94·4 (84·5 to 106·7)	22·9 (16·6 to 30·4)
9 High fasting plasma glucose	2·8 (2·4 to 3·2)	9 Ambient particulate matter	2·9 (2·4 to 3·5)	120·4 (76·2 to 180·7)	29·4 (1·8 to 62·5)
10 Drug use	2·0 (1·7 to 2·3)	10 Kidney dysfunction	2·4 (2·0 to 2·7)	62·4 (49·9 to 75·0)	−4·2 (−11·8 to 3·1)
11 Kidney dysfunction	1·9 (1·7 to 2·2)	11 Occupational injury	2·3 (2·1 to 2·6)	−21·3 (−30·0 to −11·8)	−50·4 (−55·9 to −44·5)
12 Ambient particulate matter	1·8 (1·2 to 2·3)	12 Household air pollution	1·7 (1·2 to 2·3)	−34·2 (−47·2 to −21·0)	−61·9 (−69·4 to −54·2)

E 50–74 years

Leading risks 1990	Percentage of DALYs 1990	Leading risks 2019	Percentage of DALYs 2019	Percentage change in number of DALYs, 1990–2019	Percentage change in age-standardised DALY rate, 1990–2019
1 Smoking	19·4 (18·2 to 20·6)	1 High systolic blood pressure	16·1 (14·2 to 18·0)	47·7 (36·9 to 58·0)	−28·3 (−33·6 to −23·3)
2 High systolic blood pressure	16·8 (14·9 to 18·7)	2 Smoking	15·5 (14·1 to 16·7)	22·6 (13·9 to 32·6)	−40·3 (−44·6 to −35·5)
3 Household air pollution	8·5 (6·3 to 10·7)	3 High fasting plasma glucose	12·2 (10·4 to 14·4)	127·2 (113·4 to 141·5)	10·2 (3·4 to 17·0)
4 High fasting plasma glucose	8·3 (7·0 to 9·8)	4 High body-mass index	11·8 (7·9 to 16·0)	138·4 (106·5 to 186·2)	19·1 (0·7 to 39·5)
5 High body-mass index	7·6 (4·3 to 11·6)	5 Ambient particulate matter	6·8 (5·7 to 8·0)	122·5 (78·2 to 185·1)	9·8 (−13·6 to 38·3)
6 High LDL cholesterol	7·0 (5·6 to 8·5)	6 High LDL cholesterol	6·2 (4·9 to 7·7)	37·8 (27·8 to 47·5)	−32·6 (−37·5 to −27·8)
7 Alcohol use	5·1 (4·5 to 5·7)	7 Alcohol use	5·0 (4·4 to 5·7)	51·2 (37·6 to 65·1)	−25·8 (−32·6 to −19·1)
8 Ambient particulate matter	4·7 (3·3 to 6·3)	8 Kidney dysfunction	4·7 (4·0 to 5·3)	92·8 (80·4 to 105·3)	−6·4 (−12·6 to −0·5)
9 High sodium	4·0 (1·4 to 8·0)	9 Household air pollution	3·5 (2·4 to 4·8)	−36·7 (−50·4 to −21·6)	−69·3 (−76·0 to −62·0)
10 Kidney dysfunction	3·7 (3·2 to 4·2)	10 High sodium	3·4 (1·1 to 7·1)	31·9 (−1·6 to 51·0)	−37·1 (−52·1 to −26·5)

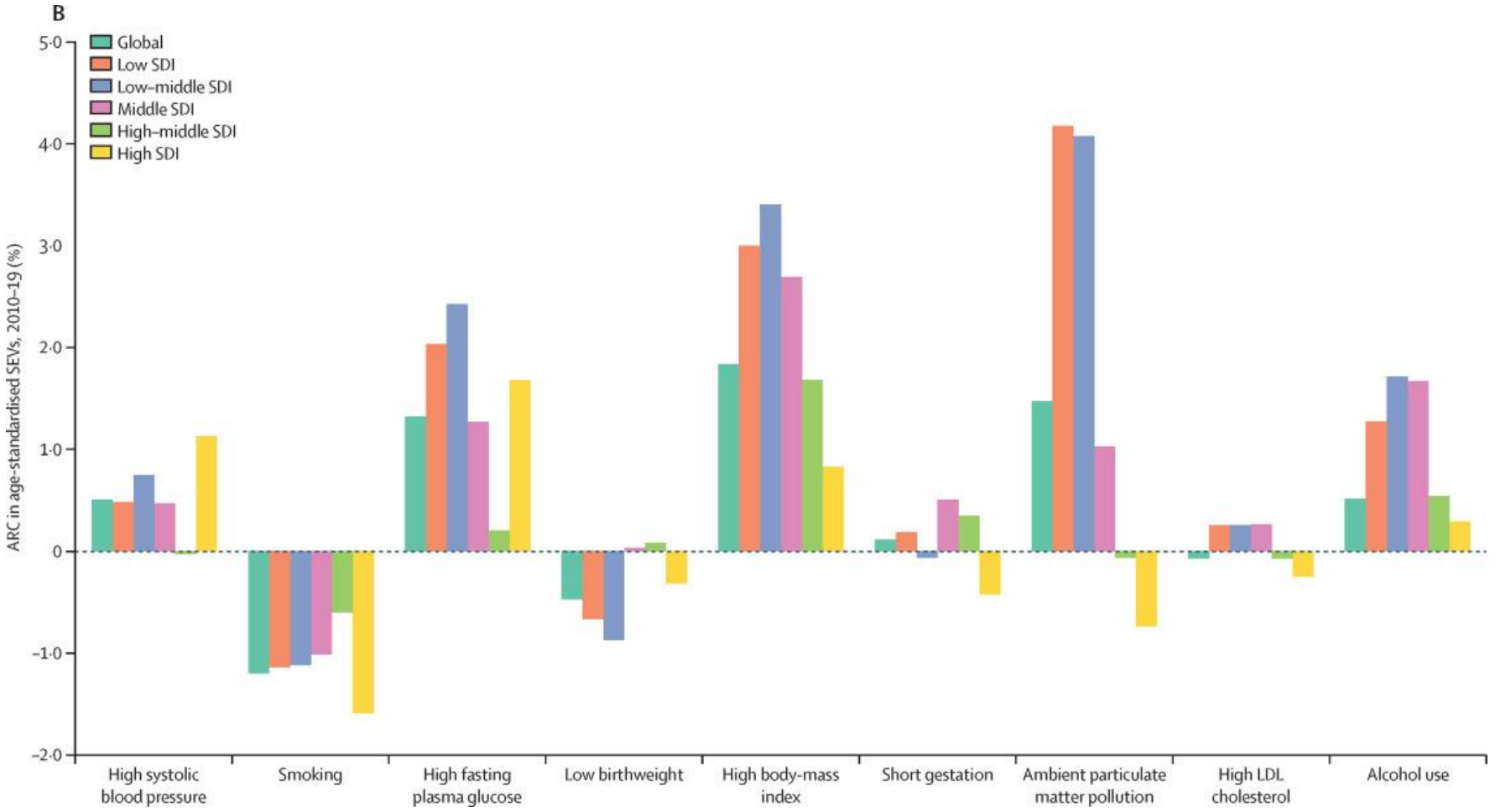
F ≥75 years

Leading risks 1990	Percentage of DALYs 1990	Leading risks 2019	Percentage of DALYs 2019	Percentage change in number of DALYs, 1990–2019	Percentage change in age-standardised DALY rate, 1990–2019
1 High systolic blood pressure	22·0 (18·6 to 25·3)	1 High systolic blood pressure	19·5 (16·3 to 22·7)	69·6 (58·6 to 80·5)	−30·0 (−34·3 to −25·7)
2 Smoking	14·8 (13·9 to 15·7)	2 High fasting plasma glucose	13·5 (10·2 to 18·0)	144·5 (130·1 to 158·7)	1·8 (−4·8 to 7·9)
3 High fasting plasma glucose	10·5 (7·8 to 14·4)	3 Smoking	12·3 (11·4 to 13·0)	58·2 (48·9 to 69·1)	−31·9 (−35·8 to −27·3)
4 High LDL cholesterol	9·2 (6·0 to 13·2)	4 High body-mass index	7·3 (4·3 to 11·1)	145·1 (123·1 to 180·2)	4·7 (−6·0 to 17·9)
5 Household air pollution	7·8 (5·7 to 10·2)	5 High LDL cholesterol	7·2 (4·5 to 10·6)	50·0 (39·2 to 58·7)	−40·2 (−43·5 to −37·1)
6 High body-mass index	5·7 (3·0 to 9·2)	6 Ambient particulate matter	6·7 (5·6 to 7·8)	143·7 (94·6 to 211·9)	4·1 (−18·2 to 31·0)
7 Ambient particulate matter	5·2 (3·7 to 6·8)	7 Kidney dysfunction	5·9 (4·9 to 6·9)	121·7 (108·6 to 134·1)	−8·6 (−14·2 to −3·6)
8 Kidney dysfunction	5·1 (4·1 to 6·1)	8 Low temperature	3·4 (2·9 to 3·9)	42·2 (32·5 to 53·1)	−41·8 (−45·7 to −37·6)
9 Low temperature	4·6 (3·9 to 5·3)	9 Household air pollution	3·1 (2·1 to 4·3)	−24·5 (−41·1 to −4·8)	−67·7 (−74·9 to −59·4)
10 Low whole grains	3·5 (1·8 to 4·4)	10 Low whole grains	3·0 (1·6 to 3·9)	66·2 (57·6 to 74·6)	−32·3 (−35·7 to −28·8)

Environmental and occupational risks
Behavioural risks
Metabolic risks

BD 2019 Risk Factors Collaborators. Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *The Lancet.* 17 October 2020. doi:10.1016/S0140-6736(20)30752-2

Annualised rate of change (ARC) for global main risk factors for DALYs

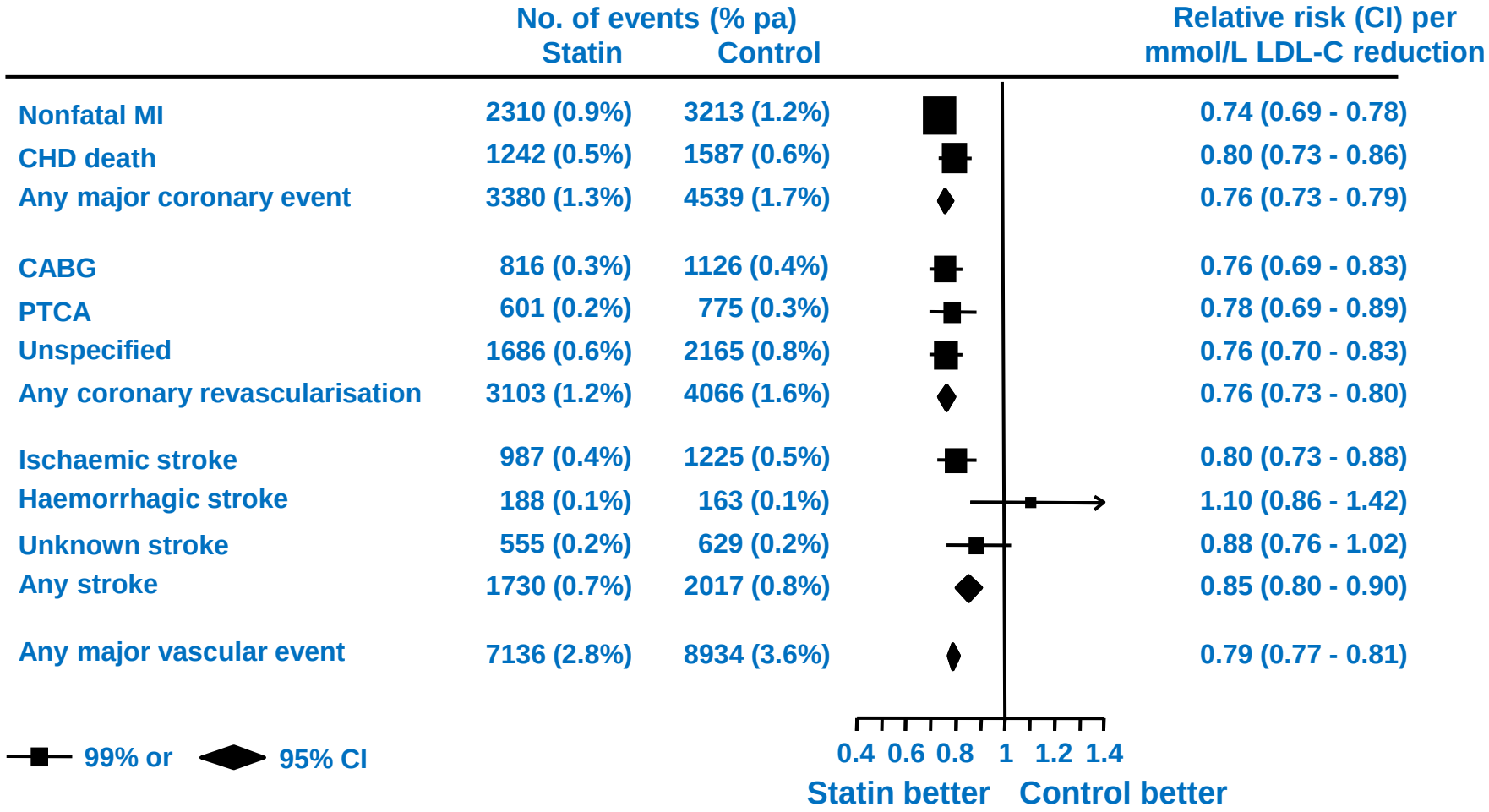


BD 2019 Risk Factors Collaborators. **Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019.** *The Lancet.* 17 October 2020. doi:10.1016/S0140-6736(20)30752-2

In terms of lipids risk there is a very large evidence-base to guide management

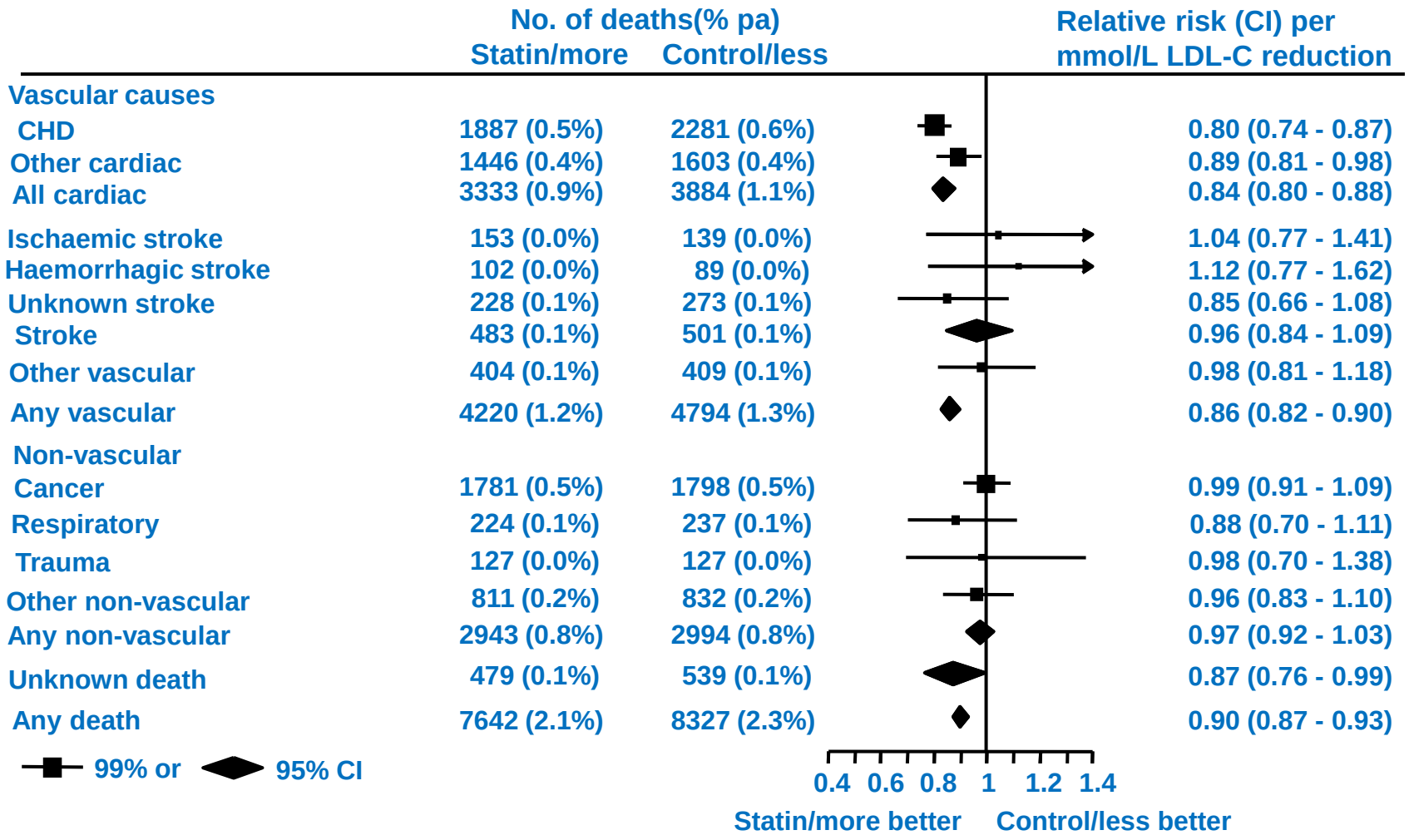
Statin vs control: Proportional effects on major vascular events per mmol/L LDL reduction

26 Mainly CVD Secondary Prevention Trials, 170,000 Subjects



CTT2. Lancet 2010;376:1670–81

Statin vs control: Proportional effects on cause-specific mortality per mmol/L LDL-C reduction



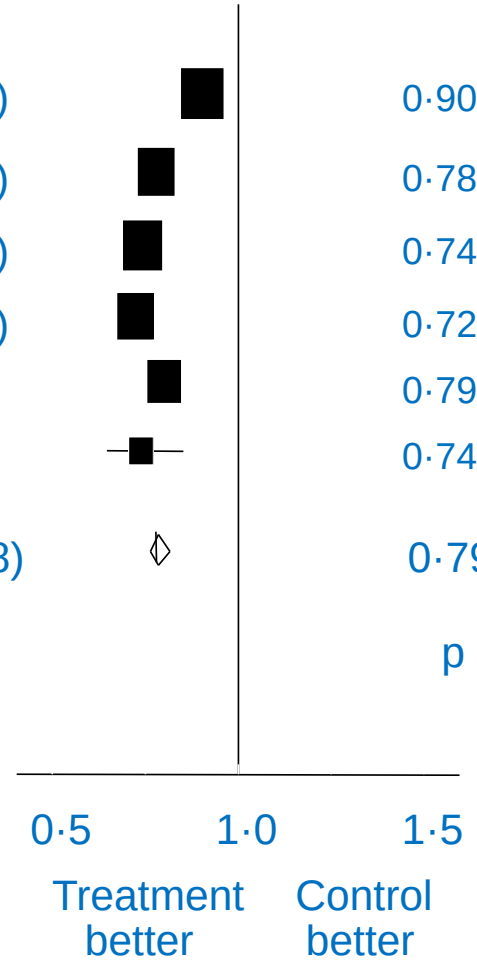
CTT2. Lancet 2010;376:1670–81

Effects on major vascular events per mmol/L LDL-C reduction by years of treatment

Year	Events (%) Treatment	Events (%) Control	RR & CI (Treatment:Control)	Rate Ratio (CI)
0-1 year	1747 (3·9)	1951 (4·3)		0·90 (0.85 – 0·96)
1-2 years	1231 (2·9)	1603 (3·8)		0·78 (0·73 – 0·83)
2-3 years	1151 (2·8)	1543 (3·9)		0·74 (0·69 – 0·79)
3-4 years	946 (2·6)	1306 (3·8)		0·72 (0·67 – 0·78)
4-5 years	811 (2·9)	993 (3·7)		0·79 (0·74 – 0·86)
5+ years	468 (2·8)	598 (3·8)		0·74 (0·67 – 0·82)
Overall	6354 (14·1)	7994 (17·8)		0·79 (0·77 – 0·81)

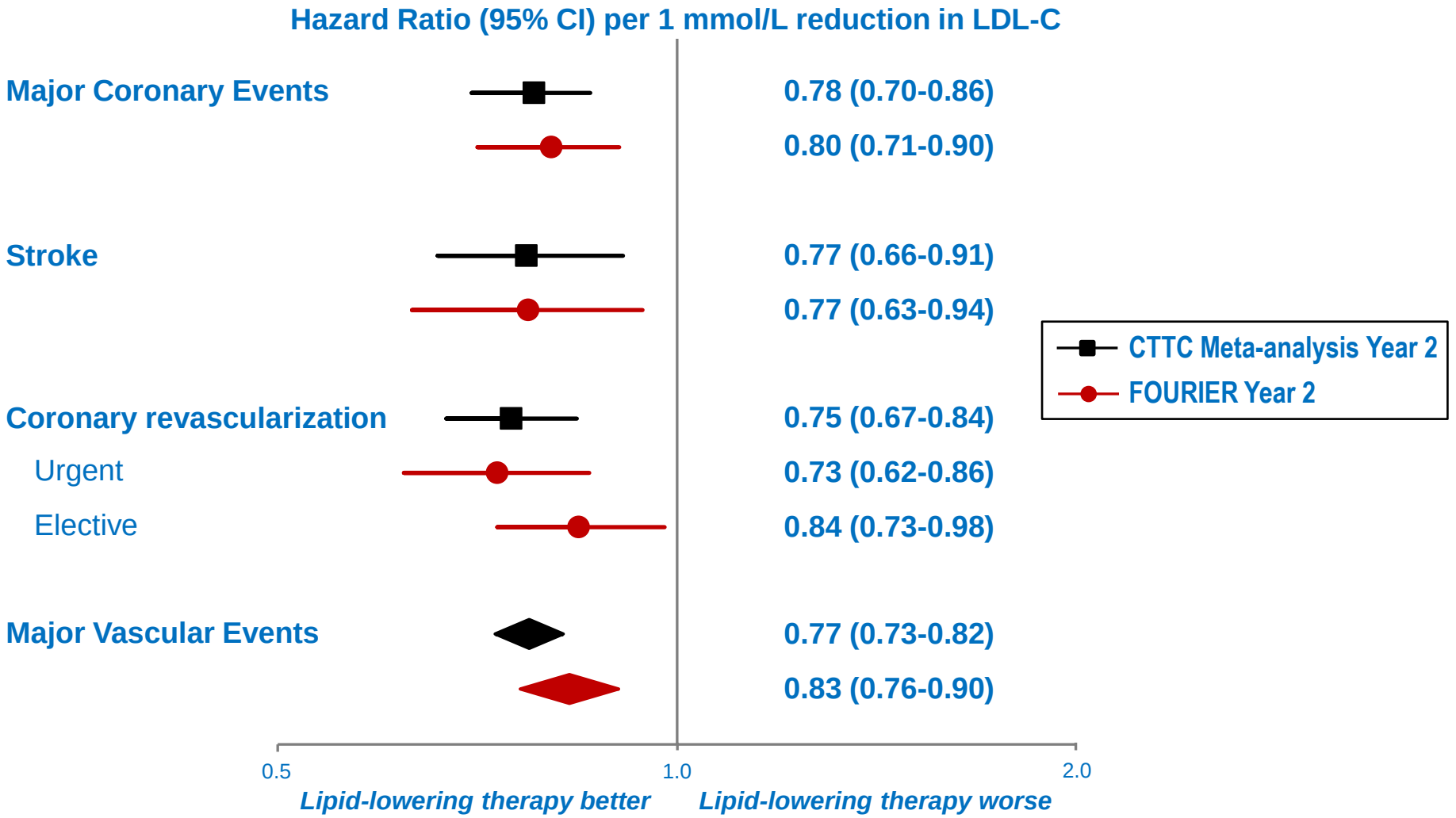
p < 0·00001

Test for trend: c^2 = 13·9; p = 0·0002



Cholesterol Trialists Collaboration, Lancet 2005

PCSK9 benefits (FOURIER) - Comparison to Cholesterol Treatment Trialists Collaboration

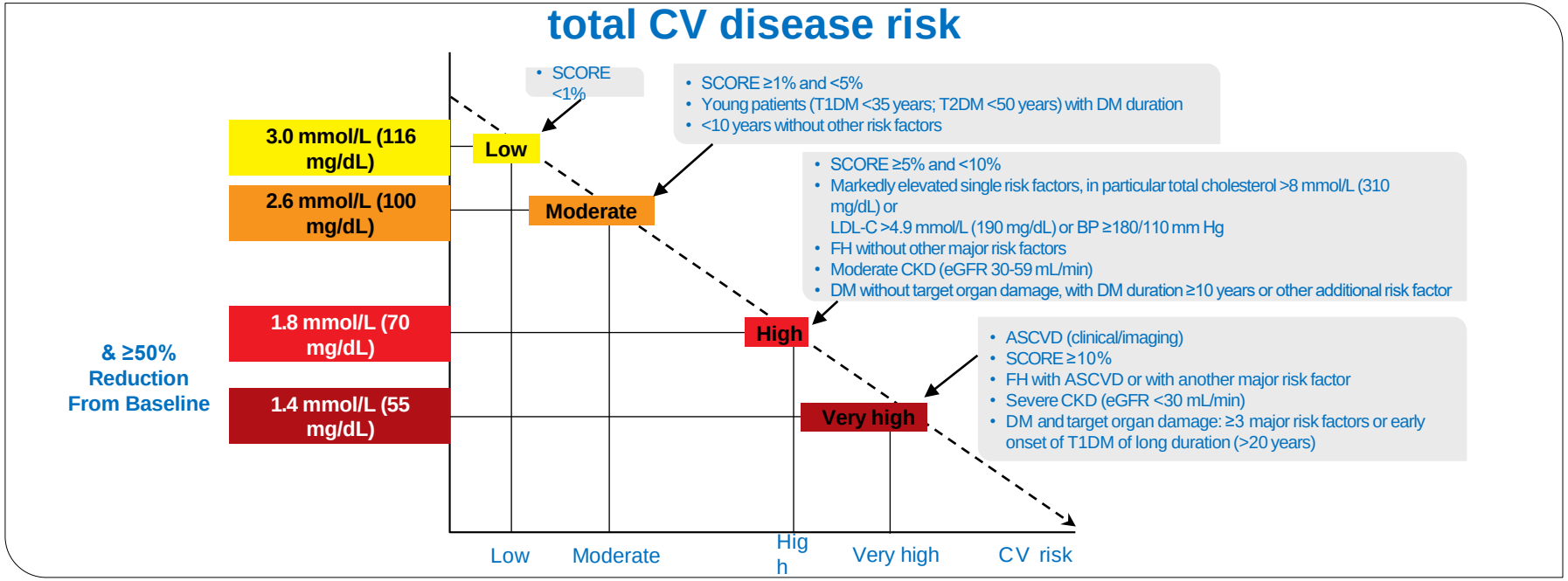


CTTC data from *Lancet* 2010;376:1670-81

ESC Guidelines 2021 for Dyslipidaemia

The ESC/EAS new LDL-C goals, and revised CV risk stratification, which are especially relevant to high- and very-high-risk patients.

Treatment goal for LDL-C across categories of total CV disease risk



ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CKD, chronic kidney disease; CV, cardiovascular; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; EAS, European Atherosclerosis Society; ESC, European Society of Cardiology; FH, familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; SCORE, Systematic Coronary Risk Estimation; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

1. Mach F, et al. *Eur Heart J*. 2020;41(1):111-188.

Substantial Risk of CHD Events Remains for Many Patients on Statin Therapy

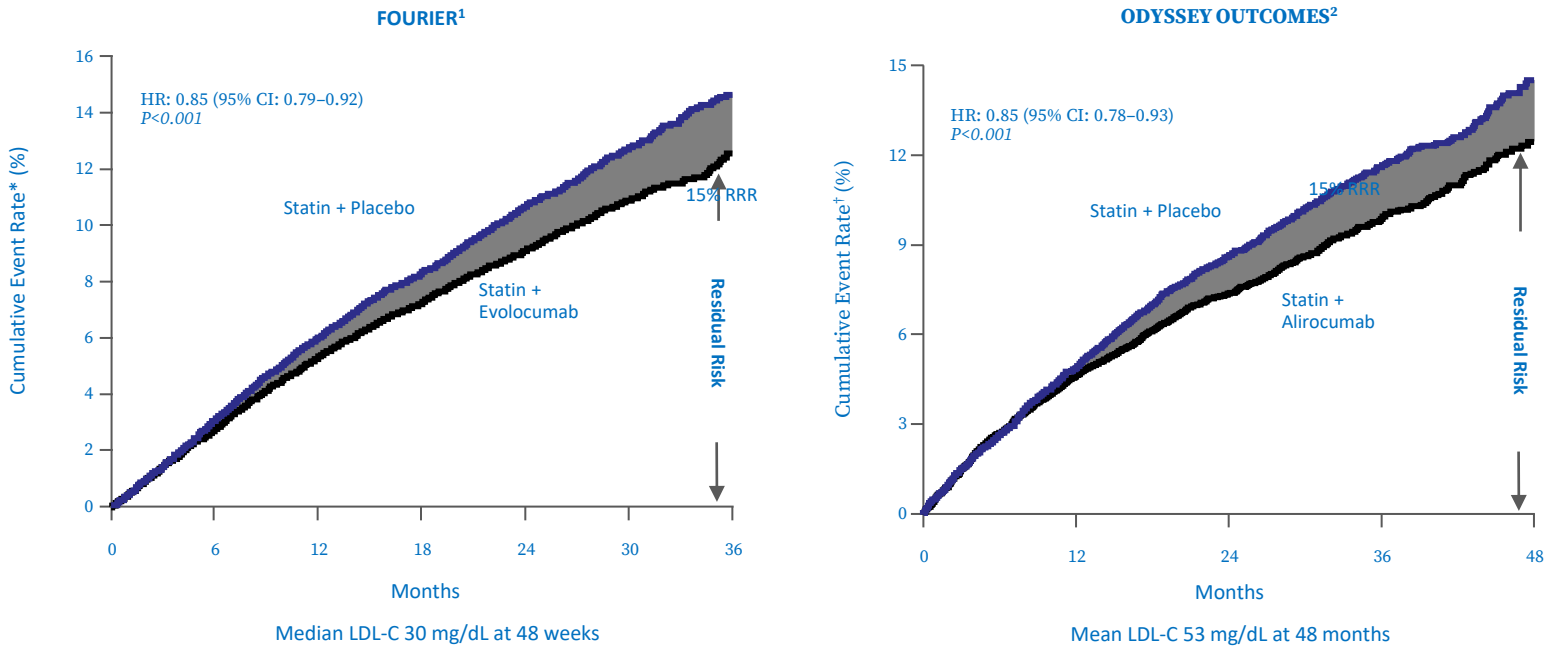
		Clinical events*	
Trial (N)	**Statin treatment**	**Risk reduction vs placebo**	**Remaining risk**
WOSCOPS** (6595)	Pravastatin 40 mg	31%	69%
AFCAPS/TexCAPS** (6605)	Lovastatin 20 or 40 mg	40%	60%
ASCOT-LLA** (10,305)	Atorvastatin 10 mg	38%	62%
4S** (4444)	Simvastatin 20 mg	26%	74%
CARE*** (4159)	Pravastatin 40 mg	24%	76%
LIPID*** (9014)	Pravastatin 40 mg	24%	76%
HPS*** (20,536)	Simvastatin 40 mg	27%	73%
PROSPER*** (5804)	Pravastatin 40 mg	24%	76%

*Nonfatal myocardial infarction and coronary heart death; **Primary prevention trial; ***Secondary prevention trial

WOSCOPS=West of Scotland Coronary Prevention Study; AFCAPS/TexCAPS=Air Force/Texas Coronary Atherosclerosis Prevention Study; ASCOT-LLA=Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm; 4S=Scandinavian Simvastatin Survival Study; CARE=Cholesterol and Recurrent Events; LIPID=Long-Term Intervention with Pravastatin in Ischemic Disease; HPS=Heart Protection Study; PROSPER=Prospective Study of Pravastatin in the Elderly at Risk

Adapted from Mahley RW, Bersot TP. In: *Goodman & Gilman's The Pharmacological Basis of Therapeutics.* 11th ed. New York: McGraw-Hill Medical Publishing Division, 2006:933–966; Bays HE. *Expert Rev Cardiovasc Ther.* 2004;2:485–501; Shepherd J et al. *N Engl J Med.* 1995;333:1301–1307; Downs JR et al. *JAMA.* 1998;279:1615–1622; Sever PS et al. *Lancet.* 2003;361:1149–1158; Scandinavian Simvastatin Survival Study Group. *Lancet.* 1994;344:1383–1389; Sacks FM et al. *N Engl J Med.* 1996;335:1001–1009; Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. *N Eng J Med.* 1998;339:1349–1357; Heart Protection Study Collaborative Group. *Lancet.* 2002;360:7–22; Shepherd J et al. *Lancet.* 2002;360:1623–1630.

Residual risk persists despite intensive LDL-C lowering with PCSK9 inhibitors



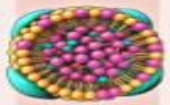
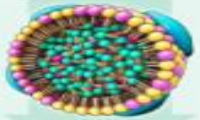
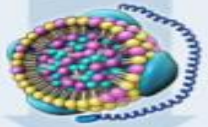
Additional risk reduction of ~15% over 2 to 4 years

*Composite of CV death, MI, stroke, hospitalisation for unstable angina or coronary revascularisation[1]; †Composite of death due to coronary heart disease, non-fatal MI, fatal or non-fatal ischaemic stroke or hospitalisation for unstable angina.[2]

CI: confidence interval; HR: hazard ratio; FOURIER: Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk; LDL-C: low density lipoprotein-cholesterol; MI: myocardial infarction; ODYSSEY-OUTCOMES: Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab; PCSK9:Proprotein convertase subtilisin/kexin type 9; RRR: relative risk reduction.

Residual CVD Risk Beyond LDL-C Lowering

Despite contemporary evidence-based therapies*, residual risk of ASCVD events persists

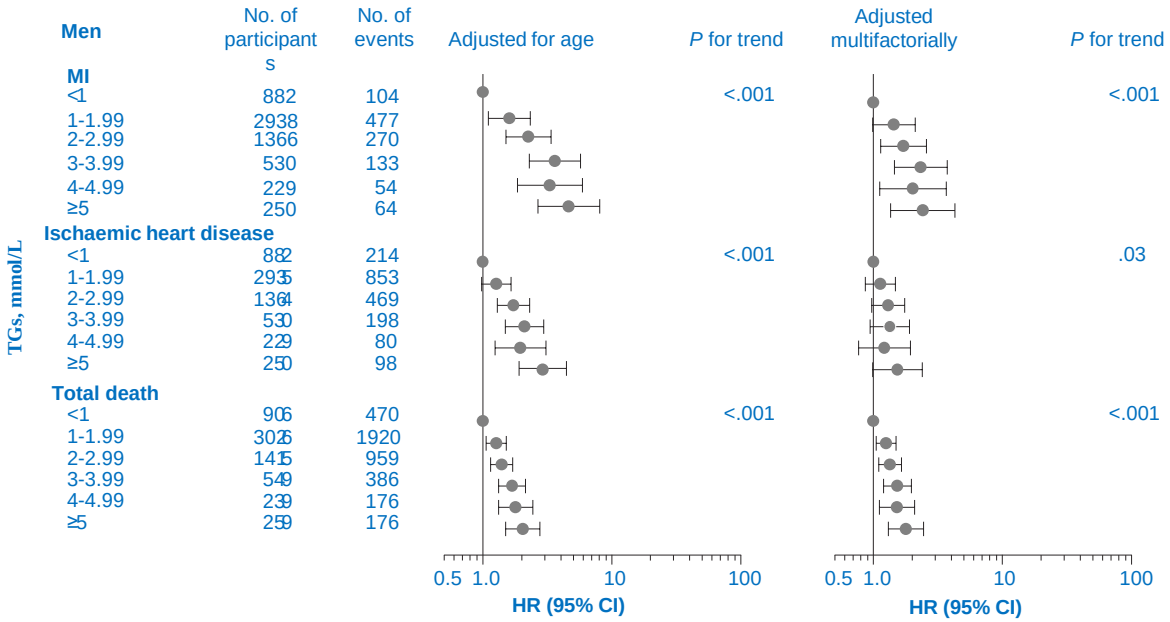
Biological Issue	Residual Cholesterol Risk	Residual Inflammatory Risk	Residual Thrombotic Risk	Residual Triglyceride Risk	Residual Lp(a) Risk	Residual Diabetes Risk
						
Critical Biomarker	LDL-C ≥100 mg/dL	hsCRP ≥2mg/L	No simple biomarker	TG ≥150mg/dL	Lp(a) ≥50mg/dL	HbA1c Fasting glucose
Potential Intervention	Targeted LDL/Apo B Reduction	Targeted Inflammation Reduction	Targeted Antithrombotic Reduction	Targeted Triglyceride Reduction	Targeted Lp(a) Reduction	SGLT2 Inhibitors GLP-1 Agonists
Randomized Trial Evidence	IMPROVE-IT FOURIER SPIRE ODYSSEY	CANTOS COLCOT *LoDoCo2* *OASIS-9*	PEGASUS COMPASS THEMIS	REDUCE-IT *PROMINENT*	Planned	EMPA-REG CANVAS DECLARE CREDENCE LEADER SUSTAIN-6 REWIND

Lawler et al. Eur Heart J 2021;42

Triglycerides as a Marker of Residual Risk

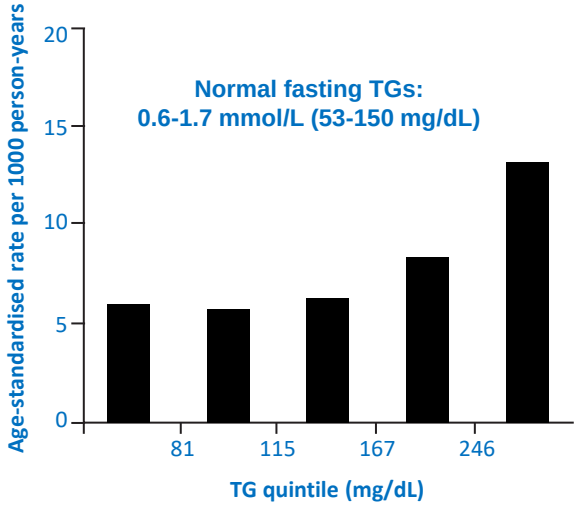
A

HRs for MI, IHD and total death by increasing levels of non-fasting TGs Near 14,000 general pop in Copenhagen Heart Study



B

20-Year CVD mortality in FU of 100 families with familial lipid disease [2]



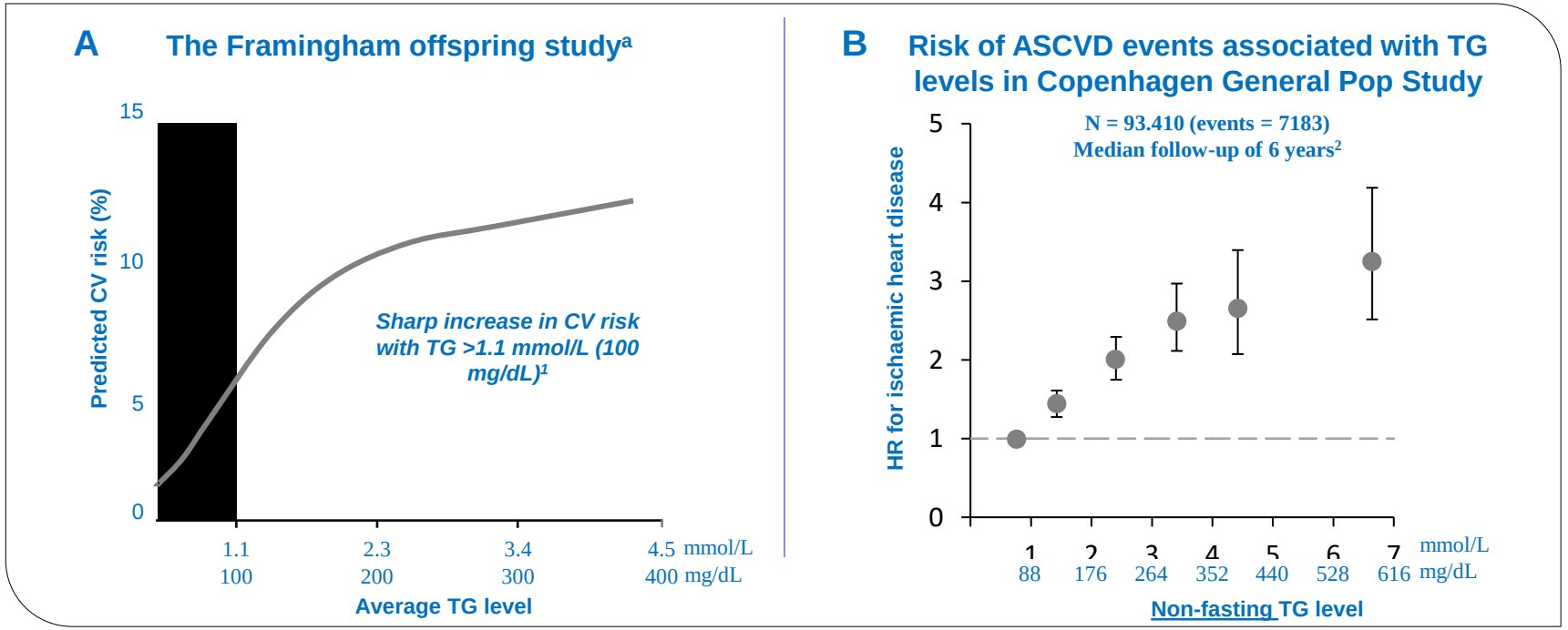
A: Correlations observed between increasing baseline levels of TG and age-standardised CVD mortality rate for relatives in all families.2

B: Familial forms of hypertriglyceridaemia are associated with premature ASCVD.

ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; HR, hazard ratio; IHD, ischaemic heart disease; MI, myocardial infarction; TG, triglyceride.

1. Nordestgaard BG, et al. *JAMA*. 2007;298(3):299-308; **2.** Austin MA, et al. *Circulation*. 2000;101(24):2777-2782.

Triglycerides as a Marker of Residual Risk



[a]N = 1336 adults aged between 53 and 57 years, free of having CVD, a 6.9% 10-year CHD Kaplan-Meier event rate and enrolled in the Framingham Offspring Study were evaluated for the association between TG and CHD events (MI, angina, revascularisation and CV death). Average TG level may be slightly better correlated with future CVD risk compared with a single or peak TG measurement. Increasing TG levels are associated with increased CV risk, even after adjusting for other potential confounders. A threshold below which increasing TG levels were not associated with increased CV risk was not identified.

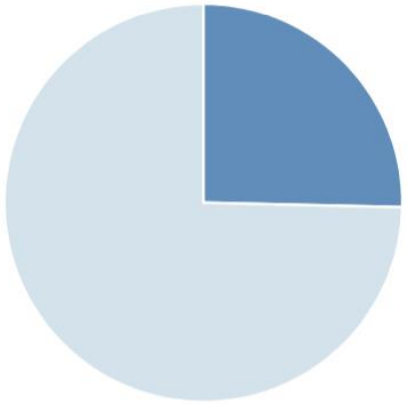
ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; HR, hazard ratio; MI, myocardial infarction; TG, triglyceride.

1. Navar AM, et al. Poster presented at: 68th Scientific Session of the ACC; March 18, 2019; New Orleans, LA; **2.** Nordestgaard BG. *Circ Res*. 2016;118(4):547-563.

Real-world risk of CV outcomes

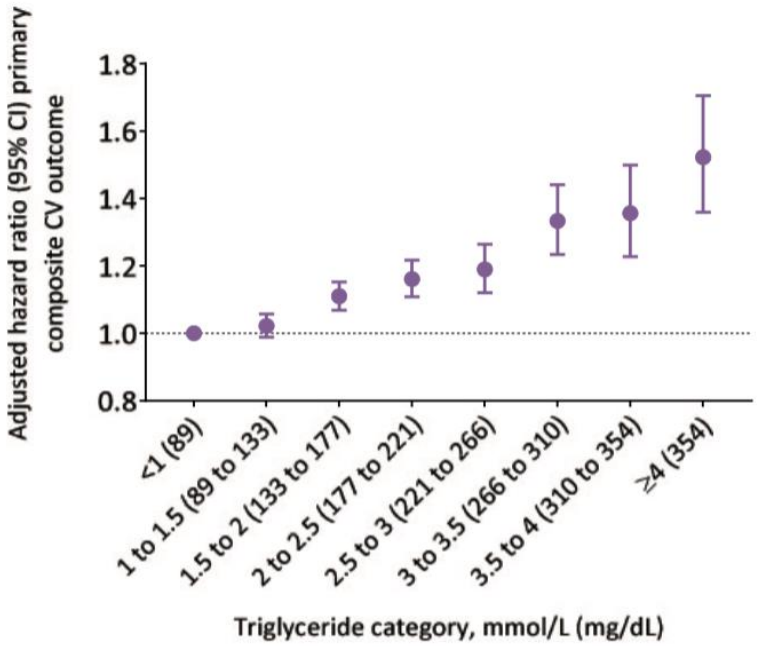
2.5M adults in Ontario with lipid panels: 25% with CVD & well-controlled LDL-C had elevated TG levels

Approximately 1 in 4 patients with ASCVD in the general population may have hypertriglyceridemia and controlled LDLc*



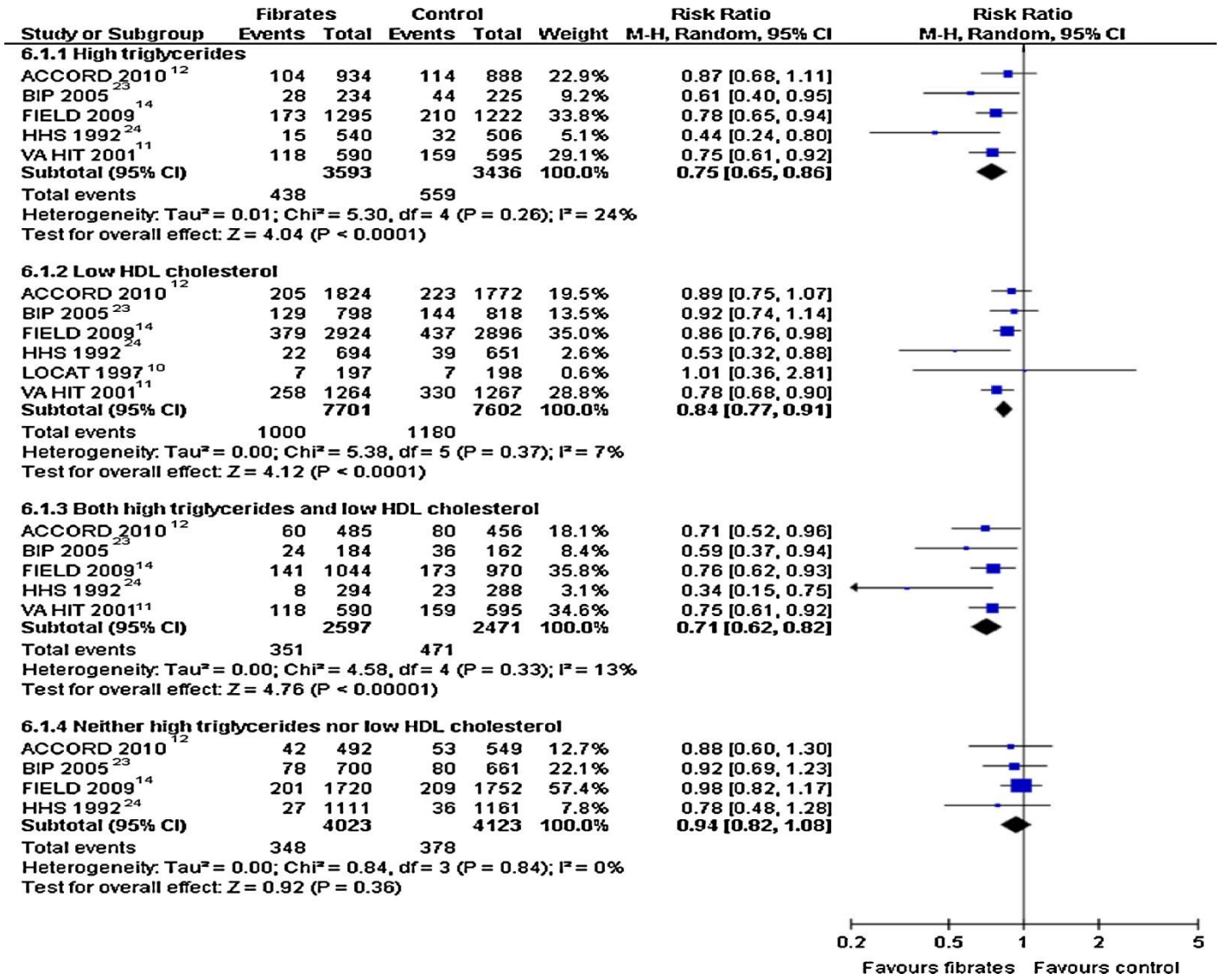
*defined as triglyceride 1.52-5.63 mmol/L (135-499 mg/dL) and LDLc 1.06-2.59 mmol/L (41-100 mg/dL)

Risk of ASCVD events associated with triglyceride level among 196,717 patients with prevalent ASCVD in the population



Lawler PR et al. Eur Heart J. 2020 Jan 1;41(1):86-94.

Efficacy of fibrates in CV risk reduction



Study or Subgroup	Fibrates Events	Fibrates Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
6.1.1 High triglycerides						
ACCORD 2010 [12]	104	934	114	888	22.9%	0.87 [0.68, 1.11]
BIP 2005 [23]	28	234	44	225	9.2%	0.61 [0.40, 0.95]
FIELD 2009 [14]	173	1295	210	1222	33.8%	0.78 [0.65, 0.94]
HHS 1992 [24]	15	540	32	506	5.1%	0.44 [0.24, 0.80]
VA HIT 2001 [11]	118	590	159	595	29.1%	0.75 [0.61, 0.92]
Subtotal (95% CI)		**3593**		**3436**	**100.0%**	**0.75 [0.65, 0.86]**
Total events	438		559			
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 5.30$, df = 4 (P = 0.26); $I^2 = 24\%$						
Test for overall effect: Z = 4.04 (P < 0.0001)						
6.1.2 Low HDL cholesterol						
ACCORD 2010 [12]	205	1824	223	1772	19.5%	0.89 [0.75, 1.07]
BIP 2005 [23]	129	798	144	818	13.5%	0.92 [0.74, 1.14]
FIELD 2009 [14]	379	2924	437	2896	35.0%	0.86 [0.76, 0.98]
HHS 1992 [24]	22	694	39	651	2.6%	0.53 [0.32, 0.88]
LOCAT 1997 [10]	7	197	7	198	0.6%	1.01 [0.36, 2.81]
VA HIT 2001 [11]	258	1264	330	1267	28.8%	0.78 [0.68, 0.90]
Subtotal (95% CI)		**7701**		**7602**	**100.0%**	**0.84 [0.77, 0.91]**
Total events	1000		1180			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.38$, df = 5 (P = 0.37); $I^2 = 7\%$						
Test for overall effect: Z = 4.12 (P < 0.0001)						
6.1.3 Both high triglycerides and low HDL cholesterol						
ACCORD 2010 [12]	60	485	80	456	18.1%	0.71 [0.52, 0.96]
BIP 2005 [23]	24	184	36	162	8.4%	0.59 [0.37, 0.94]
FIELD 2009 [14]	141	1044	173	970	35.8%	0.76 [0.62, 0.93]
HHS 1992 [24]	8	294	23	288	3.1%	0.34 [0.15, 0.75]
VA HIT 2001 [11]	118	590	159	595	34.6%	0.75 [0.61, 0.92]
Subtotal (95% CI)		**2597**		**2471**	**100.0%**	**0.71 [0.62, 0.82]**
Total events	351		471			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.58$, df = 4 (P = 0.33); $I^2 = 13\%$						
Test for overall effect: Z = 4.76 (P < 0.00001)						
6.1.4 Neither high triglycerides nor low HDL cholesterol						
ACCORD 2010 [12]	42	492	53	549	12.7%	0.88 [0.60, 1.30]
BIP 2005 [23]	78	700	80	661	22.1%	0.92 [0.69, 1.23]
FIELD 2009 [14]	201	1720	209	1752	57.4%	0.98 [0.82, 1.17]
HHS 1992 [24]	27	1111	36	1161	7.8%	0.78 [0.48, 1.28]
Subtotal (95% CI)		**4023**		**4123**	**100.0%**	**0.94 [0.82, 1.08]**
Total events	348		378			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.84$, df = 3 (P = 0.84); $I^2 = 0\%$						
Test for overall effect: Z = 0.92 (P = 0.36)						

Lee M, Efficacy of fibrates for CV risk reduction: a meta-analysis. Atherosclerosis, 2011

Summary

- CVD most important cause of premature death and disability
- Traditional risk factors explain most observed CVD risk
- Major evidence base for interventions on LDL, smoking, BS and BP
- But significant residual CVD risk remains
- Renewed interest in raised triglycerides as a marker for residual risk