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SAFETY OF LOW LEVELS OF LDL-CHOLESTEROL

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BACKGROUND

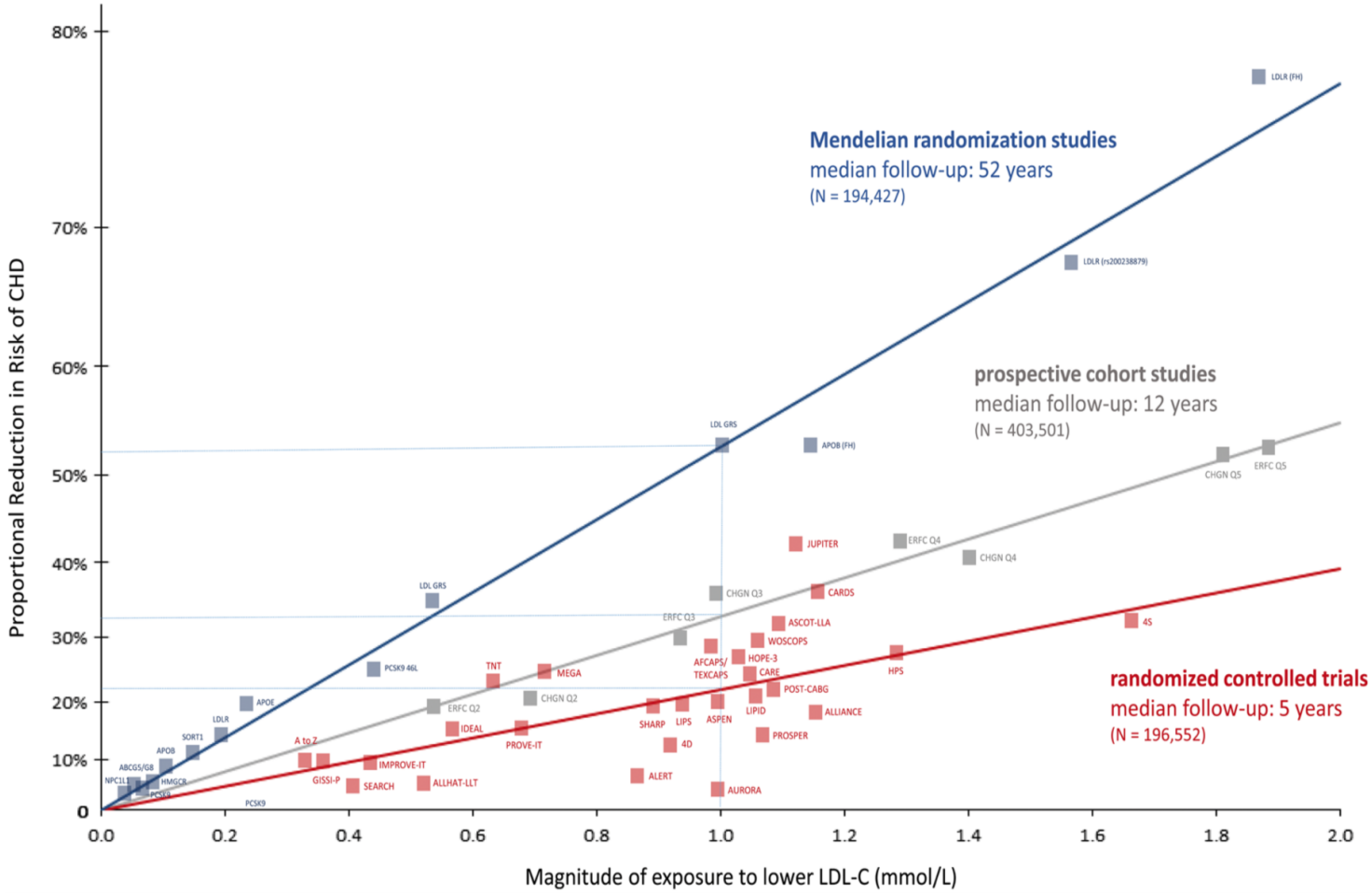
- Low-density lipoprotein cholesterol (LDL-C) is well established as a major cardiovascular (CV) risk factor
- Accumulating evidence supports a linear association between LDL-C levels and CV risk
- However, the lower limit of LDL-C that might offer CV benefits without any safety concerns is still a topic of debate
- Moreover, there are concerns about lowering cholesterol too much, since data show an association with an increased risk for cancer, intracranial haemorrhage, neurocognitive disorders and all-cause mortality
- The safety of pharmacological treatment to very low levels of LDL-C is becoming increasingly important with highly effective lipid-lowering drugs such as PCSK9 inhibitors

PCSK9, proprotein convertase subtilisin/kexin type 9

Ference BA, et al. Eur Heart J. 2017;38(32):2459-72; Faselis C, et al. Curr Pharm Des. 2018;24(31):3658-64; Zhou L, et al. BMJ Open 2020; 10: e036976

LDL-C: MAIN FACTOR IN THE DEVELOPMENT OF ATHEROSCLEROSIS

REDUCTION IN RISK OF CV EVENTS WITH LOWERING OF LDL-C



CHD, coronary heart disease; LDL-C, low density lipoprotein cholesterol

Ference B, et al. Eur Heart J. 2017;38(32):2459-72

RECOMMENDED TREATMENT GOALS FOR LDL-C LOWERING THERAPY

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2016 VS 2019 ESC GUIDELINES

Risk category	LDL-C goals (starting with untreated LDL-C)	
	2016	2019
Very-high risk	<1.8 mmol/L (70 mg/dL) or ≥50% ↓ if LDL-C 1.8–3.5 mmol/L (70–135 mg/dL)	<1.4 mmol/L (55 mg/dL) and ≥50% ↓
High-risk	<2.6 mmol/L (100 mg/dL) or ≥50% ↓ if LDL-C 2.6–5.2 mmol/L (100–200 mg/dL)	<1.8 mmol/L (70 mg/dL) and ≥50%↓
Moderate-risk	<3.0 mmol/L (115 mg/dL)	<2.6 mmol/L (100 mg/dL)
Low-risk	<3.0 mmol/L (115 mg/dL)	<3.0 mmol/L (115 mg/dL)

For patients with ASCVD experiencing a second vascular event within 2 years while taking maximally tolerated statin, an LDL-C goal of <1.0 mmol/L (<40 mg/dL) should be considered

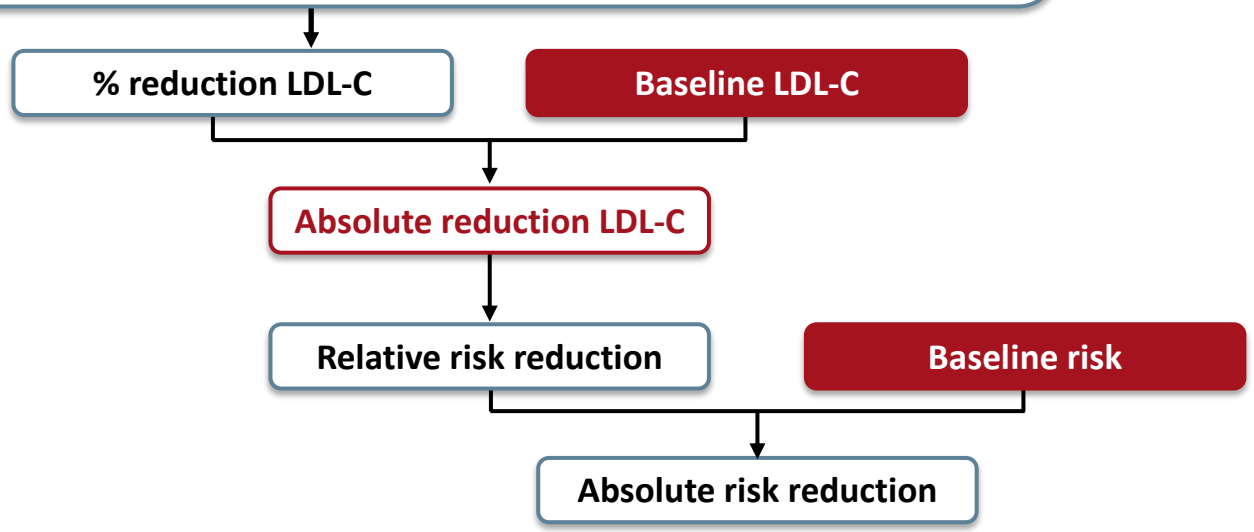
ASCVD, atherosclerotic cardiovascular disease; ESC, European society of cardiology; LDL-C, low density lipoprotein cholesterol

Adapted from: Catapano AL, et al. Eur Heart J. 2016;37:2999-3058; Mach F, et al. Eur Heart J. 2020;41(1):111-88

EXPECTED CLINICAL BENEFITS OF LDL-C LOWERING THERAPIES

Intensity of lipid lowering treatment

Treatment	Average LDL-C reduction
Moderate intensity statin	~ 30%
High intensity statin	~ 50%
High intensity statin plus ezetimibe	~ 65%
PCSK9 inhibitor	~ 60%
PCSK9 inhibitor plus high intensity statin	~ 75%
PCSK9 inhibitor plus high intensity statin plus ezetimibe	~ 85%



LDL-C, low density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9

Mach F, et al. Eur Heart J. 2020;41(1):111-88

PHYSIOLOGICAL ASPECTS OF LDL

- **Low-density lipoprotein** (LDL) is the final step of the lipoprotein metabolism cascade and **is the vehicle by which cholesterol is delivered to peripheral tissues** through LDL receptors
- **All mammalian cells** have the capacity to **synthesize their own cholesterol**. Tissues requiring high cholesterol intake (e.g. adrenal glands for hormone synthesis) usually have supplemental sources other than LDL
- The **liver is the main organ receiving LDL particles**
  - Approximately 3 out of 4 LDL particles finish their metabolic life in the liver
  - The **hepatic LDL/LDL-R system is**, along with HDL, the **main pathway to excrete cholesterol** with bile into the faeces, which is almost the only mechanism to get rid of cholesterol
  - **When the LDL-LDL-R pathway is not efficient enough, LDL accumulates** and infiltrates the artery wall, **inducing *atheroma* plaque formation**

LDL-R, LDL, low density lipoprotein receptor

Masana L. Rev Esp Cardiol (Engl Ed). 2018;71(7):591-2

POPULATIONS INDICATING SAFETY OF LOW LEVELS OF LDL

Newborn[1,2]

- LDL-C: 0.7-1.8 mmol/L
- maximum growth acceleration, maturation of the central nervous system

"Natural" populations (South America, Africa)[3,4]

- total cholesterol: ~2 - 4 mmol/L
- related to diet and other lifestyle factors

Intensive lipid-lowering therapy[5]

- combination therapy (e.g. statins with ezetimibe/PCSK9 inhibitor)
- PCSK9 inhibitors

Genetic disorders causing extremely low LDL-levels

- e.g. loss-of-function variants in *PCSK9*[6]
- often associated with reduction of coronary events[7]

LDL, low density lipoprotein; LDL-C, low density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9

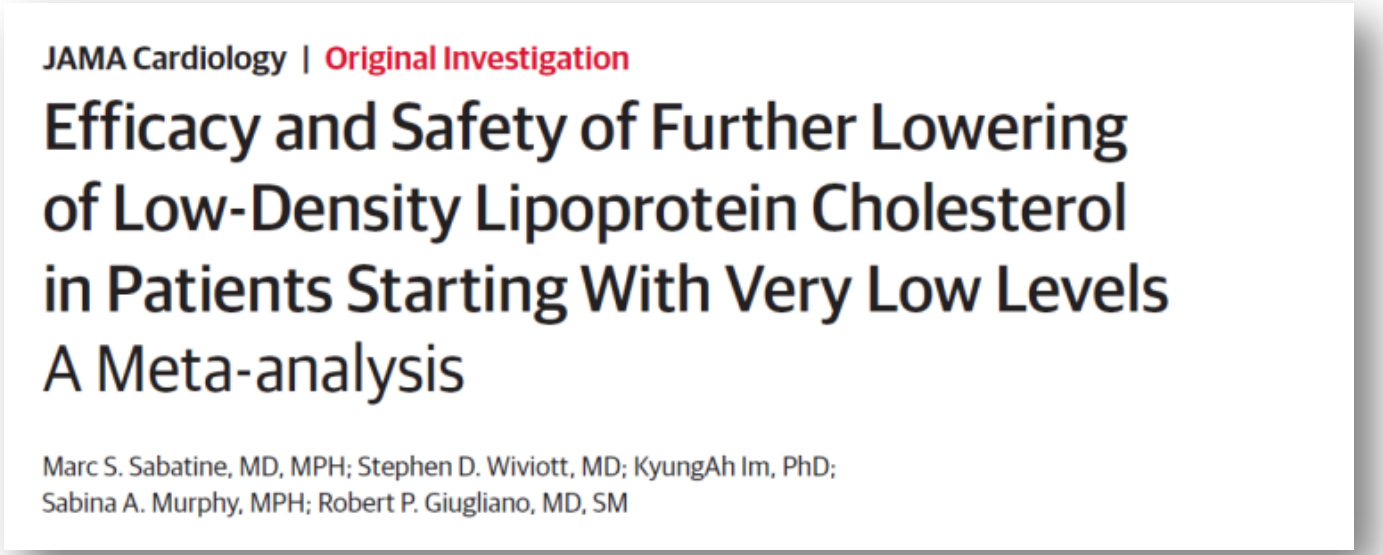
1. O'Keefe JH, et al. J Am Coll Cardiol. 2004; 43:2142-46; 2. Dietschy J, et al. J Clin Lipdol. 2004; 45: 1375-1397; 3. Kaplan H, et al. Lancet. 2017;389(10080):1730-9; 4. Shaper AG, et al. Int J Epidemiol. 2012;41(5):1221-5; 5. Preiss D, et al. JACC 2020; 75: 1945-1955; 6. Kent S, et al. Circ Cardiovasc Genet. 2017;10(4):e001632; 7. Cohen JC, et al. N Engl J Med. 2006;354(12):1264-72

NATURALLY VERY LOW LDL-C LEVELS

- Mutations in genes associated with the regulation of LDL-C levels including *low-density lipoprotein receptor (LDL-R), HMGCR, apolipoprotein E (APOE)* and *PCSK9*
  - associated with naturally low LDL-C levels
- **Loss of function mutations in PCSK9**
  - Occur in 1-3% of the human population
  - Associated with naturally low LDL-C levels and reduced CVD risk
    - **ARIC Study**
      - A total of 12,887 individuals (3363 black and 9525 white subjects) who were followed for 15 years
      - included *PCSK9* loss-of-function mutation carriers
        - CHD risk reduction was 88% in black and 47% in white *PCSK9* loss-of-function mutation carriers
        - no changes in overall mortality rates
        - incidence of cancer or haemorrhagic stroke not reported

ARIC, Atherosclerosis risk in communities; CHD, coronary heart disease; CVD, cardiovascular disease; HMGCR, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase; LDL-C, low density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9

McCormack T, et al. Int J Clin Pract. 2016;70(11):886-97; Cohen JC, et al. N Engl J Med. 2006;354(12):1264-72



- Meta-analysis of statin and nonstatin therapy
- Data sources:
  - Statins – CTTC meta-analysis
  - Non-statins:
    - IMPROVE-IT trial (ezetimibe)
    - FOURIER (evolocumab)
    - REVEAL (anacetrapib)

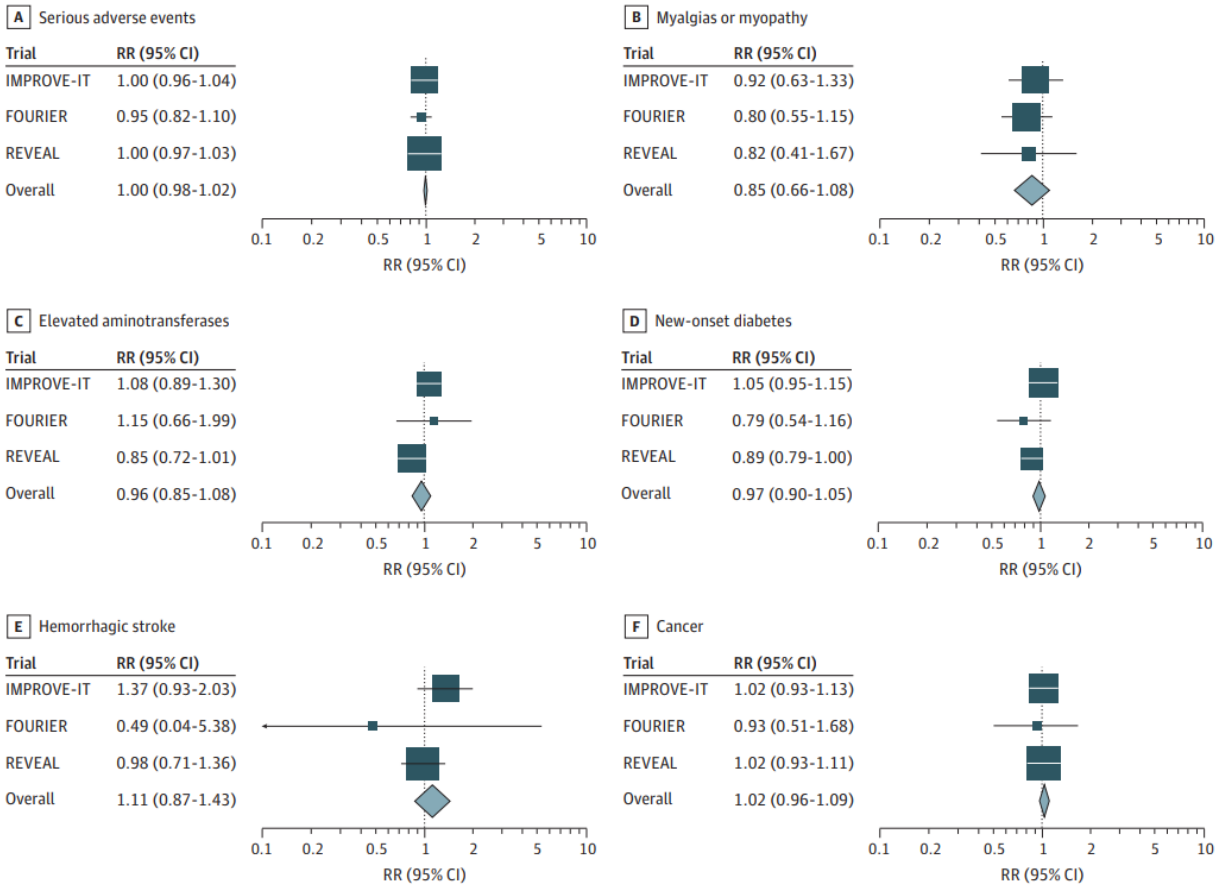
Trial characteristics

Trial	No. of participants	Type of intervention	Drug	Achieved LDL-C, mmol/L		Median duration of follow-up, y	Overall no. of major vascular events
				Control arm	Experimental arm		
CTTC (<2 mmol/L)	NR	HMGCR inhibitor (statin)	Various	1.7	NR	4.9	1,922
IMPROVE-IT	18,144	NPC1L1 inhibitor	Ezetimibe	1.8	1.4	6.0	5,104
FOURIER (<1.8 mmol/L)	2,034	PCSK9 inhibitor	Evolocumab	1.7	0.5	2.1	184
REVEAL	30,449	CETP inhibitor	Anacetrapib	1.6	1.4	4.1	4,282

CETP, cholesteryl ester transfer protein; CTTC, cholesterol treatment trialists collaboration; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; LDL-C, low density lipoprotein cholesterol; NPC1L1, Niemann-Pick C1-Like 1; PCSK9, proprotein convertase subtilisin/kexin type 9

Sabatine MS, et al. JAMA Cardiol. 2018;3(9):823-8

SAFETY OUTCOMES IN NON-STATIN TRIALS



	Patients with event, no.		Meta-analysis data	
Safety outcome	**Experimental arm**	**Control arm**	**Risk ratio (95% CI)**	**p value**
Any serious adverse event	12,809	12,836	1.00 (0.98-1.02)	0.89
Myalgias or myopathy	116	135	0.85 (0.66-1.08)	0.19
Aminotransferase elevation	488	510	0.96 (0.85-1.08)	0.48
New-onset diabetes	1,272	1,320	0.97 (0.90-1.05)	0.46
Haemorrhagic stroke	132	118	1.11 (0.87-1.43)	0.40
Cancer	1,747	1,715	1.02 (0.96-1.09)	0.55

- *In summary, there is a **consistent relative risk reduction in major vascular events per further reduction in LDL-C** in patient populations **starting as low as a median of 1.6 mmol/L** (63mg/dL) **and achieving levels as low as a median of 0.5 mmol/L** (21 mg/dL), with no **offsetting adverse effects***
- *These data suggest **further lowering of LDL-C thresholds for initiating more intensive therapy,** or simply **targeting LDL-C at least as low as approximately 0.5 mmol/L** or 20 mg/dL, **would further reduce CV risk***

CI, confidence interval; CV, cardiovascular; LDL-C, low density lipoprotein cholesterol; RR, risk ratio

Sabatine MS, et al. JAMA Cardiol. 2018;3(9):823-8

NEUROCOGNITIVE DISORDERS AND LOW LDL-C

- The brain is the most cholesterol-rich organ in the body and constitutes approx. 25% of the body's cholesterol
  - Cholesterol is an essential component for neuronal physiology
- Cholesterol metabolism in brain is independent from that in peripheral tissues due to the blood-brain barrier and cholesterol levels must be accurately maintained in order to keep brain function well
- Defects in brain cholesterol metabolism has been linked to neurodegenerative diseases, such as Alzheimer's disease, Huntington's disease, Parkinson's disease, and some cognitive deficits typical of the old age

LDL-C, low density lipoprotein cholesterol

Björkhem I, et al. Arterioscler Thromb Vasc Biol. 2004:24:806-15; Zhang J et al. Protein Cell. 2015;6(4):254-64; Olsson AG et al. J Intern Med. 2017;281(6):534-53

NEUROCOGNITIVE DISORDERS AND LOW LDL-C

STATINS

- **Systematic review and meta-analysis of short and long-term cognitive effects[1]**
  - 11 studies (3 short-term, 8 long-term)
  - patients without baseline cognitive dysfunction
  - **Short-term cognition studies**
    - **short-term trials did not show a consistent effect of statins on cognition**
  - **Long-term cognition studies**
    - **long-term data may support a beneficial role for statins in the prevention of dementia**
    - 23,443 pts; mean exposure to statins: 3 to 24.9 years
    - 3 studies found no association between statin use and incident dementia; 5 studies found a favourable effect
    - pooled results revealed a 29% reduction in incident dementia in statin-treated patients; HR 0.71 (95% CI 0.61-0.82)

PCSK9 INHIBITORS

- **Patients with primary hypercholesterolaemia - a meta-analysis[2]**
  - **increased incidence of neurocognitive adverse events in patients on PCSK9i** [OR 2.34 (95% CI 1.11-4.93), *P* = 0.02] compared with placebo
- **FOURIER trial[3]**
  - 22,655 patients, median follow-up 2.2 years
  - proportions of patients reporting **cognitive decline at the end of the study were similar for placebo versus evolocumab**
- **EBBINGHAUS trial (sub-study of FOURIER patients)[4]**
  - 1,204 patients; median follow-up 19 months
  - **no significant difference in cognitive function observed between evolocumab and placebo** treatment groups
- **PCSK9i therapy is unlikely to cause cognitive impairment in short-term follow-up**. Longer follow-up and more diverse trial populations are needed

CI, confidence interval; HR, hazard ratio; LDL-C, low density lipoprotein cholesterol; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; OR, odds ratio; pts, patients

1. Swiger KJ, et al. Mayo Clin Proc. 2013;88(11):1213-21; 2. Lipinski MJ, et al. Eur Heart J. 2016;37:536-45; 3. Gencer B, et al. J Am Coll Cardiol. 2020;75:2283-93; 4. Giugliano RP, et al. N Engl J Med. 2017;377:633-43

SUMMARY

- Elevated LDL-C is clearly an established major risk factor for the development of atherosclerotic cardiovascular disease (ASCVD)
  - Risk reduction is proportional to the absolute and relative LDL-C reduction achieved
- Intensive lipid-lowering therapy (using combination therapy and especially PCSK9 inhibitors) achieves very low levels of LDL-C
- Achieving very low levels of LDL-C provides additional clinical benefit in reducing the incidence of ASCVD and is not associated with serious side effects

LDL-C, low density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9

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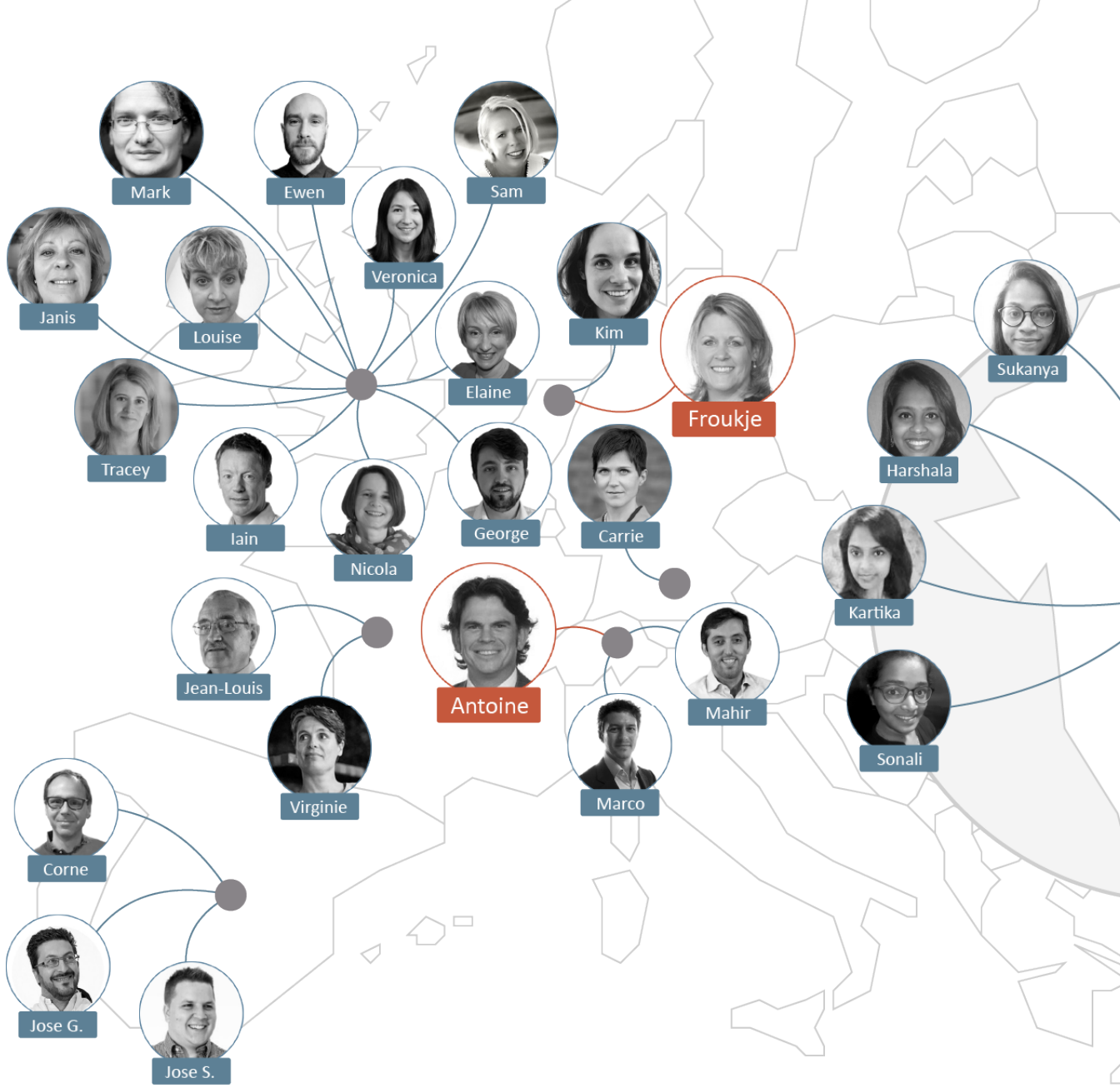

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