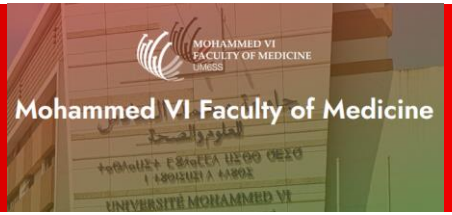


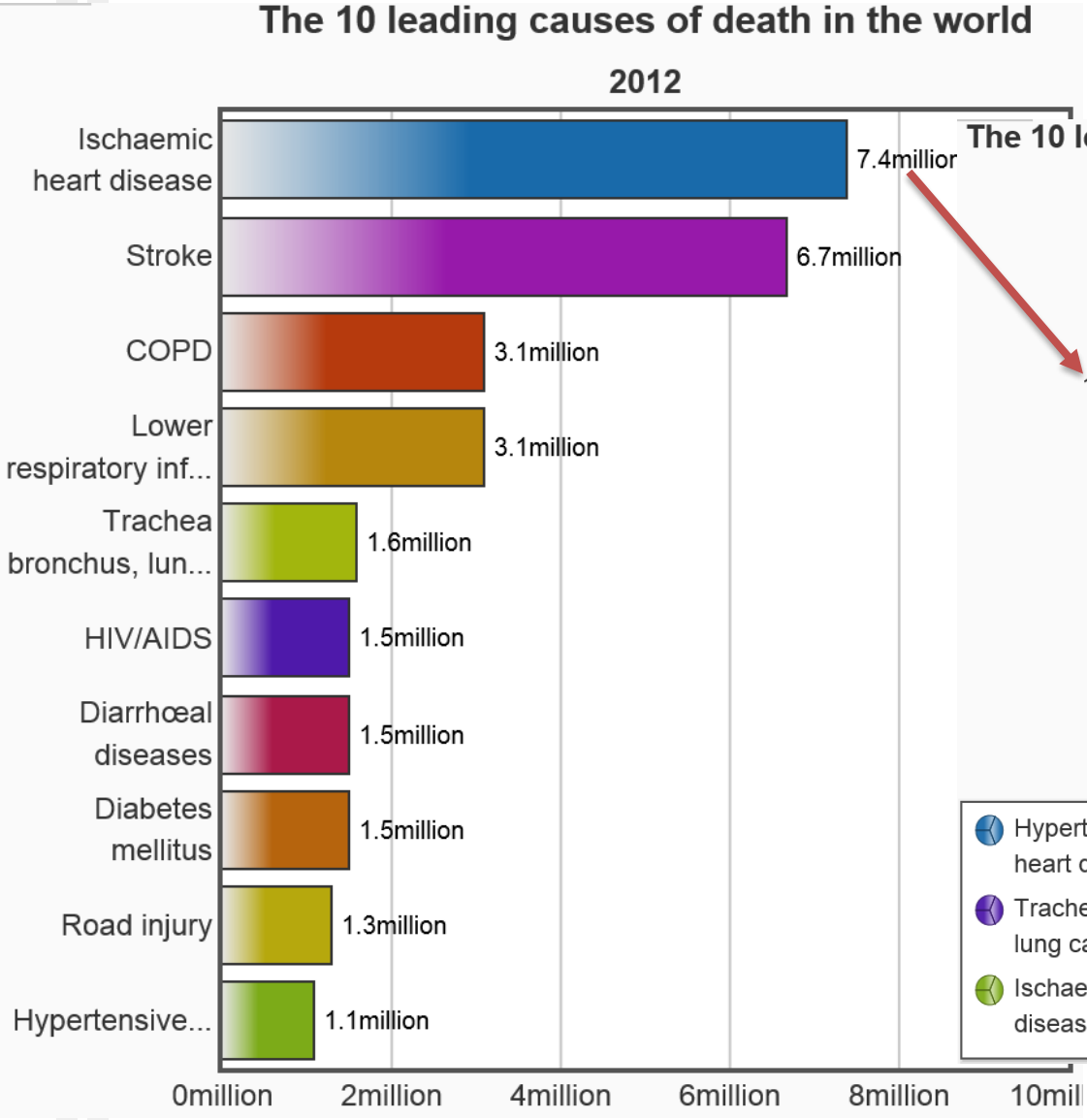
Epidemiology, Prevention and Risk Factors for Atherosclerosis

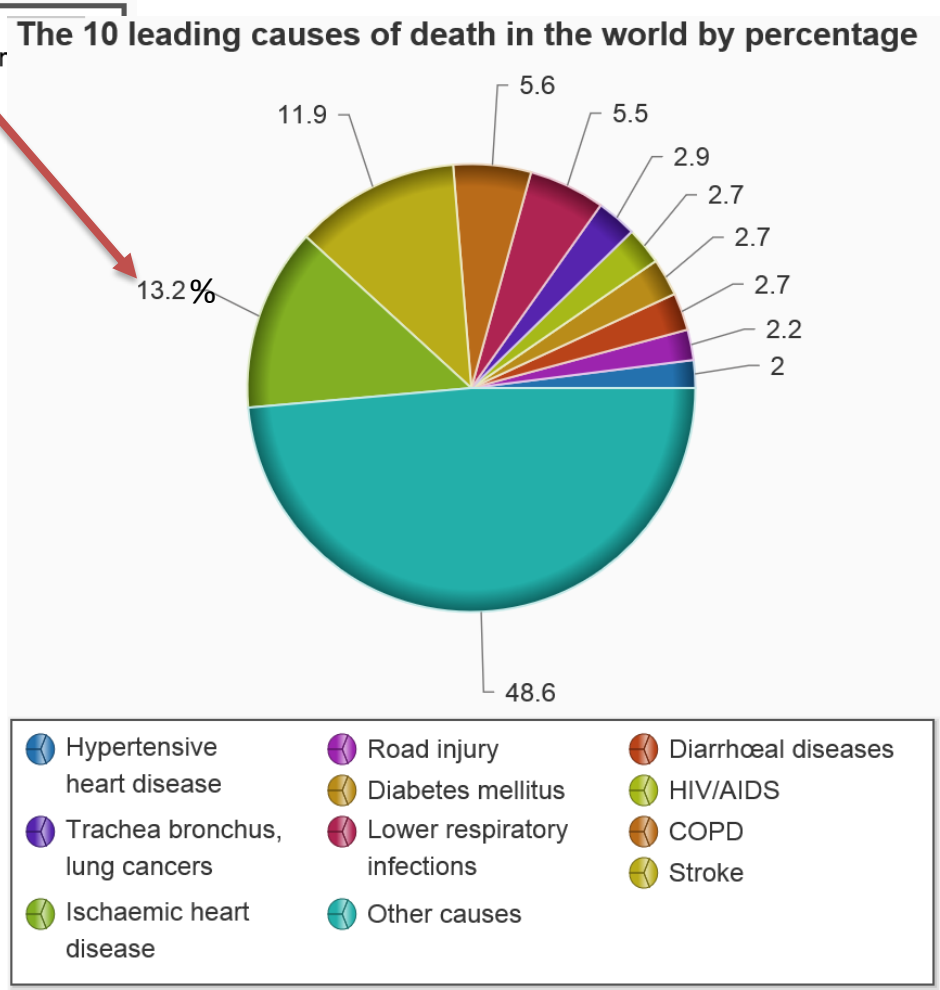
Prof Stéphane Carlier
Department of Cardiology, UMons

Plan

- **Epidemiology**
- **Risk factors, including air pollution**
- **Pathophysiology of Atherosclerosis**
- **ESC Recommendations Prevention and Dyslipidemia**

Global Epidemiology





http://www.who.int/mediacentre/factsheets/fs310/en/

Circulation

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Supplemental Material

2024 Heart Disease and Stroke Statistics: A Report of US and Global Data From the American Heart Association

Seth S. Martin, Aaron W. Aday, Zaid I. Almarzooq, Cheryl A.M. Anderson, Pankaj Arora, Christy L. Avery, Carissa M. Baker-Smith, Bethany Barone Gibbs, Andrea Z. Beaton, Amelia K. Boehme, Yvonne Commodore-Mensah, Maria E. Currie, Mitchell S.V. Elkind, Kelly R. Evenson, Giuliano Generoso, Debra G. Heard, Swapnil Hiremath, Michelle C. Johansen, ... See all authors

Originally published 24 Jan 2024 | https://doi.org/10.1161/CIR.0000000000001209 | Circulation. 2024;0

Supplemental data

Global CVD Statistics Supplement

Europe and Central Asia CVD Statistics Supplement

High-Income Countries CVD Statistics Supplement

Latin America and Caribbean CVD Statistics Supplement

North Africa and Middle East CVD Statistics Supplement

South Asia CVD Statistics Supplement

Southeast and East Asia and Oceania CVD Statistics Supplement

Sub-Saharan Africa CVD Statistics Supplement

Deaths from cardiovascular diseases

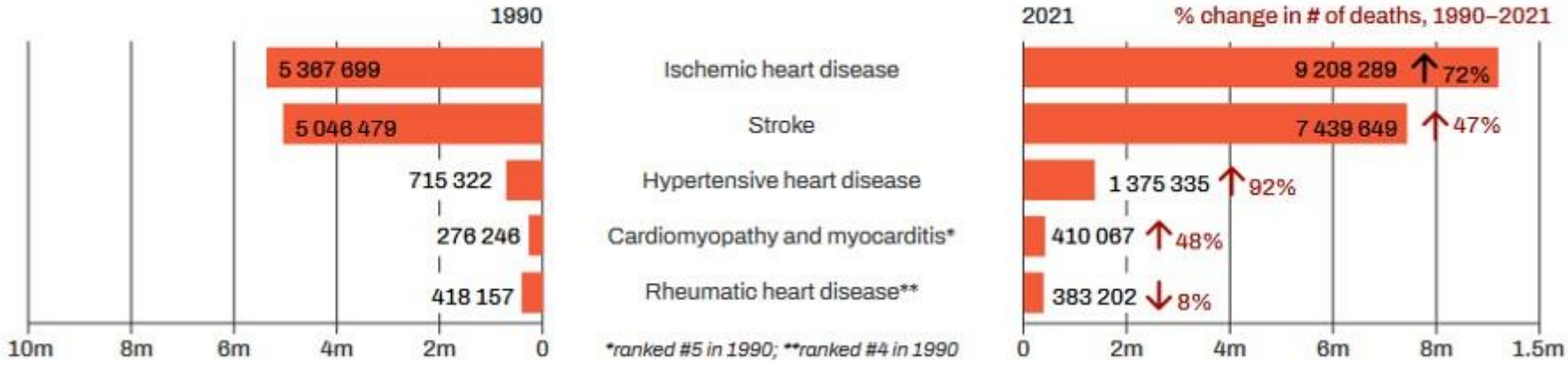
1990

12 345 727

2021

19 906 615

Top 5 causes of cardiovascular disease deaths, 1990 and 2021[1]



Deaths from cardiovascular diseases regionwide

1990

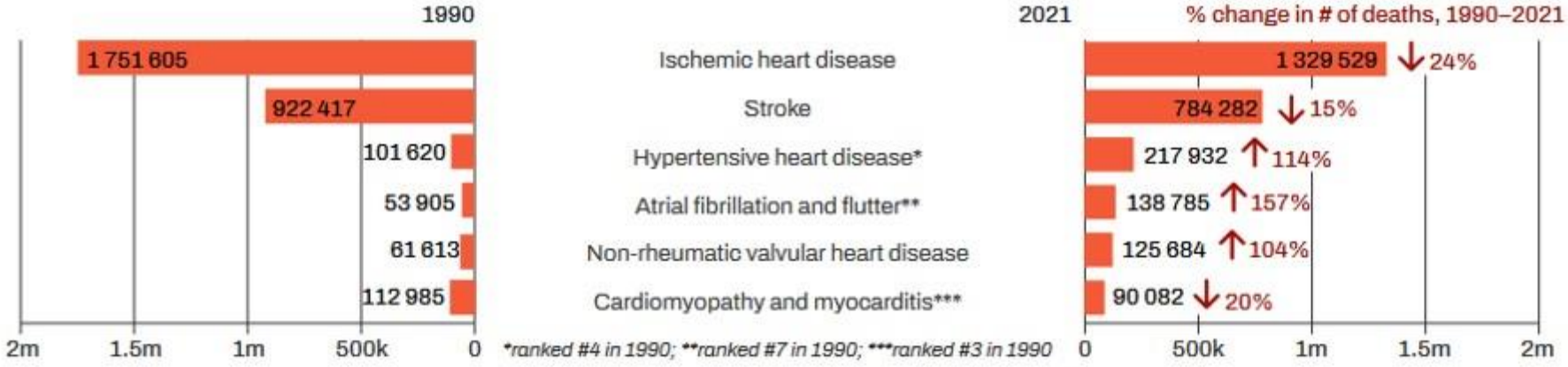
3 179 162

2021

2 930 969

[1]*Andorra, Argentina, Australia, Austria, Belgium, Brunei Darussalam, Canada, Chile, Cyprus, Denmark, Finland, France, Germany, Greece, Greenland, Iceland, Ireland, Israel, Italy, Japan, Luxembourg, Malta, Monaco, Netherlands, New Zealand, Norway, Portugal, Republic of Korea, San Marino, Singapore, Spain, Sweden, Switzerland, United Kingdom, United States of America, Uruguay*

Top causes of cardiovascular disease deaths, 1990 and 2021[2]



*ranked #4 in 1990; **ranked #7 in 1990; ***ranked #3 in 1990

North Africa and Middle East[1]

Deaths from cardiovascular diseases regionwide

1990

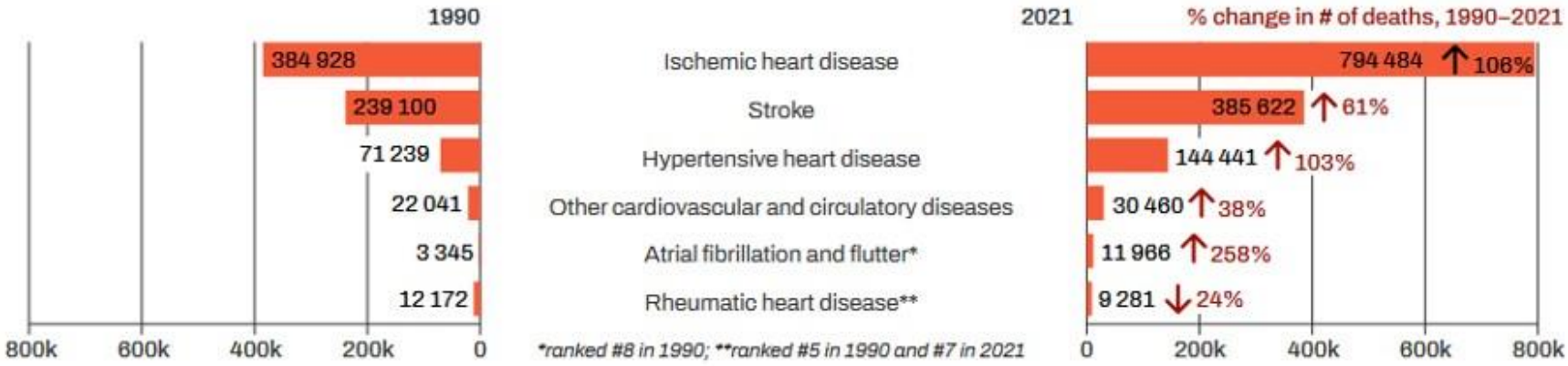
749 569

2021

1 403 267

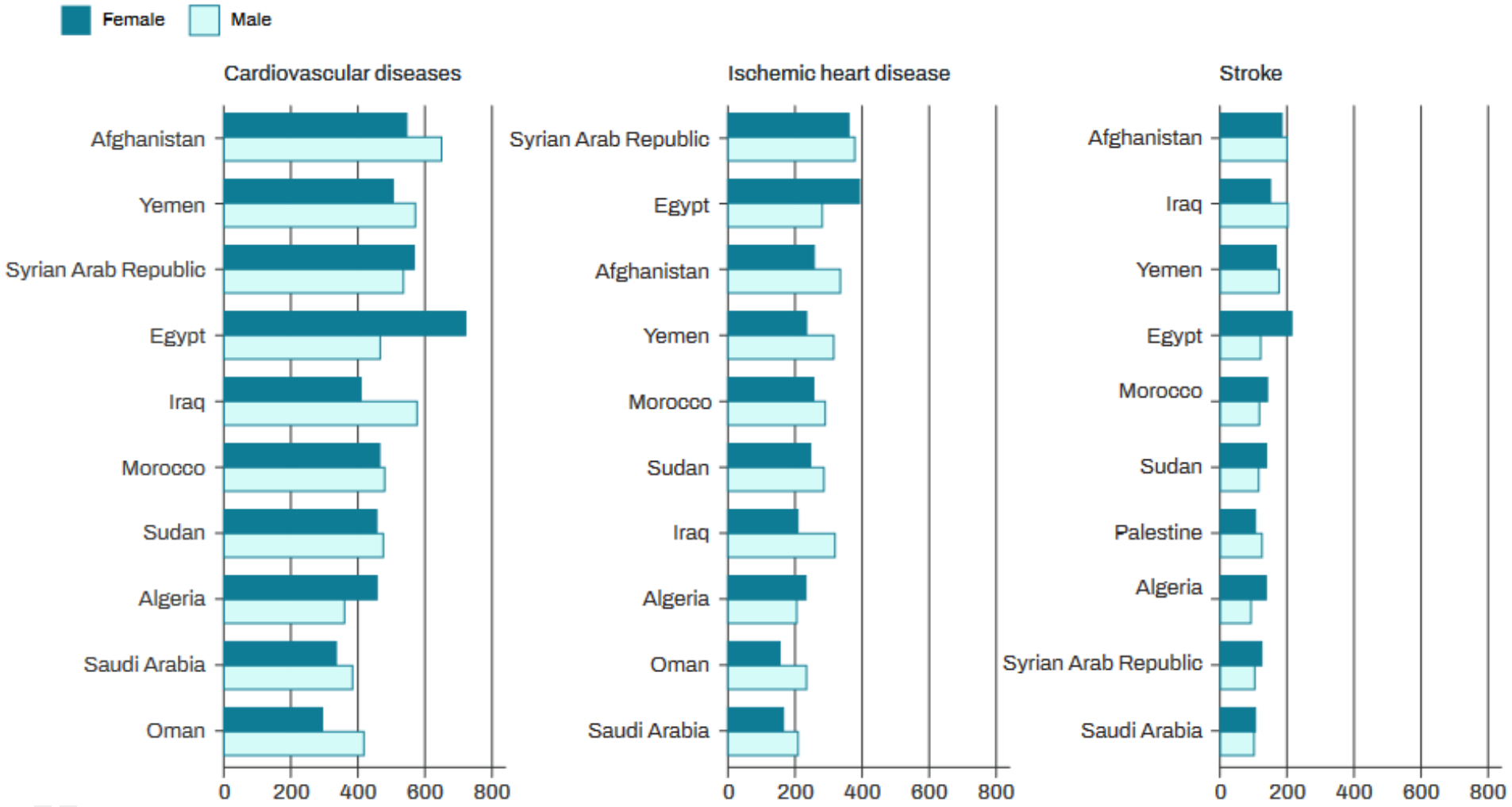
[1]*Afghanistan, Algeria, Bahrain, Egypt, Iran (Islamic Republic of), Iraq, Jordan, Kuwait, Lebanon, Libya, Morocco, Oman, Palestine, Qatar, Saudi Arabia, Sudan, Syrian Arab Republic, Tunisia, Türkiye (Turkey), United Arab Emirates, Yemen*

Top causes of cardiovascular disease deaths, 1990 and 2021[2]



**ranked #8 in 1990; **ranked #5 in 1990 and #7 in 2021*

Age-standardized cardiovascular disease, ischemic heart disease, and stroke death rates by country (top 10) per 100 000 persons, 2021



Ongoing issues

- Tobacco use remains a major public health problem and is no longer declining
- Smoking in women
- Fruit and vegetable consumption is increasing, but fat consumption is stable
- Not enough exercise performed
- Obesity remains far too prevalent
- Diabetes is becoming a pandemic, increasing by ~50% in some countries

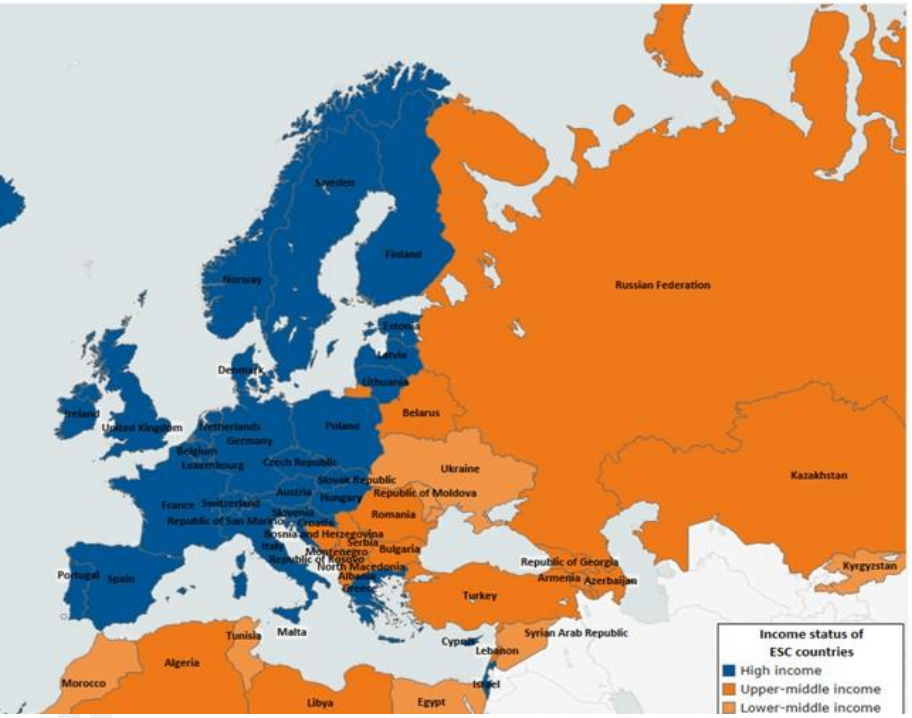
Cardiovascular Disease Statistics

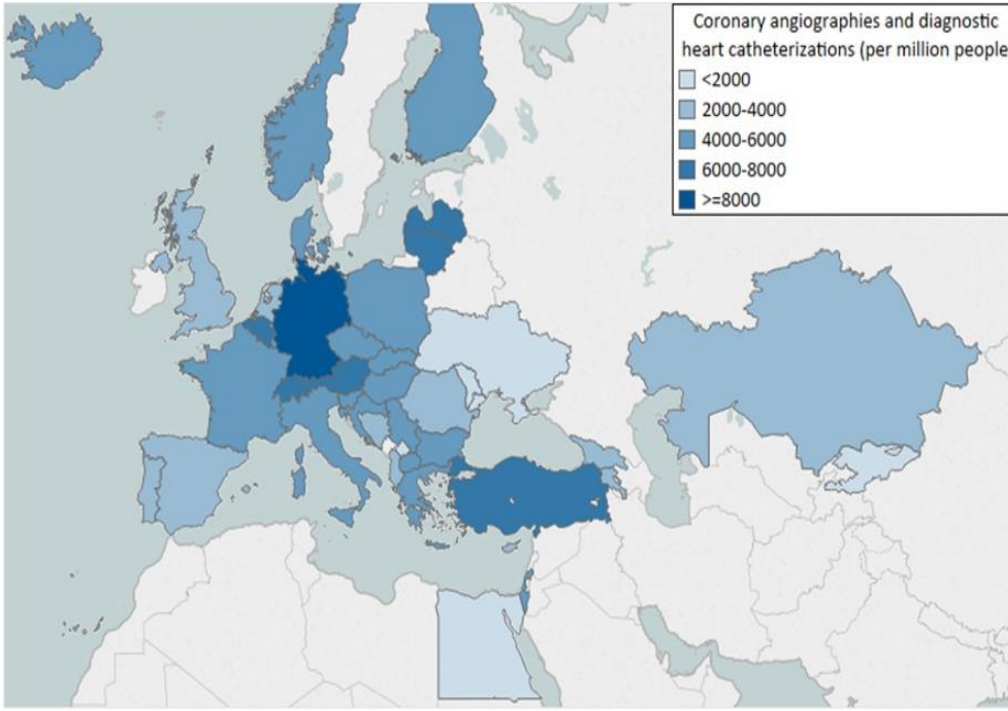
ESC European Society of Cardiology

European Heart Journal (2020) **41**, 12–85
doi:10.1093/eurheartj/ehz859

SPECIAL ARTICLE
Coronary artery disease

European Society of Cardiology: Cardiovascular Disease Statistics 2019





Mortality

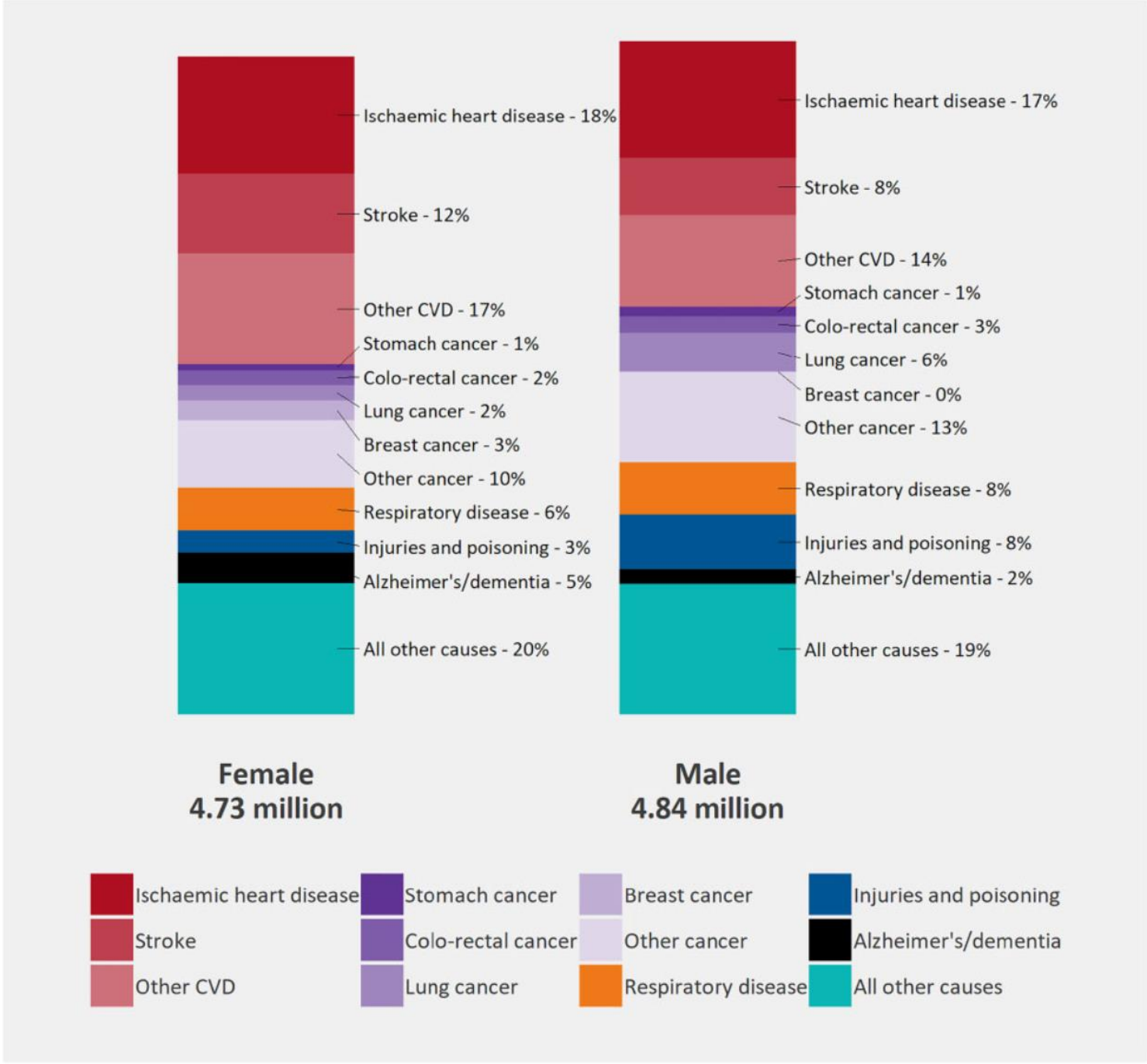


Figure 50 Deaths by cause for all ages in ESC member countries (latest year available). *Data source*: WHO Mortality Database, https://www.who.

Early mortality (<70 years)

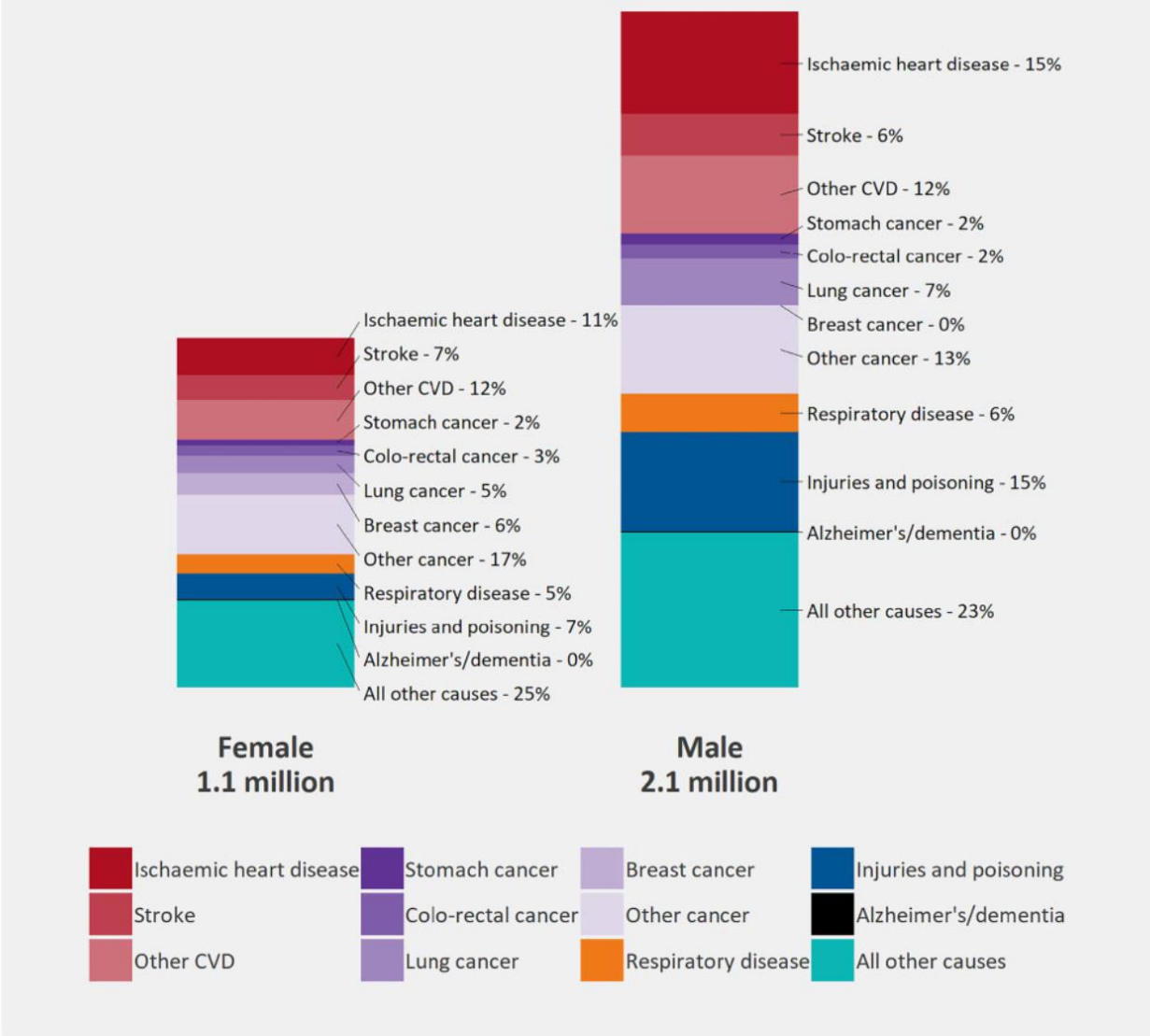
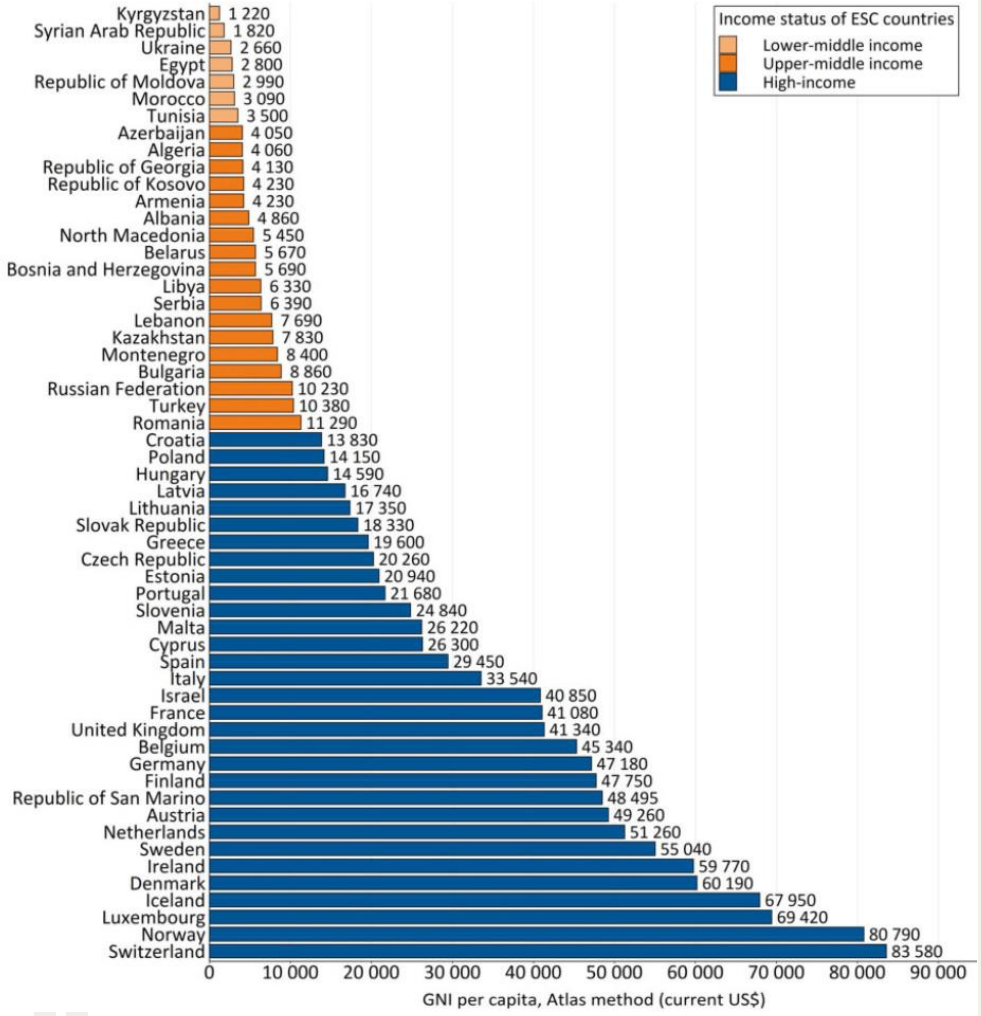


Figure 52 Premature deaths by cause for all ages in ESC member countries (latest year available). *Data source*: WHO Mortality Database, https://www.who.int/healthinfo/statistics/mortality_rawdata/en. *Data not available*: Algeria, Lebanon, Libya, Republic of Kosovo, and Republic of San Marino

Cardiovascular mortality and Income



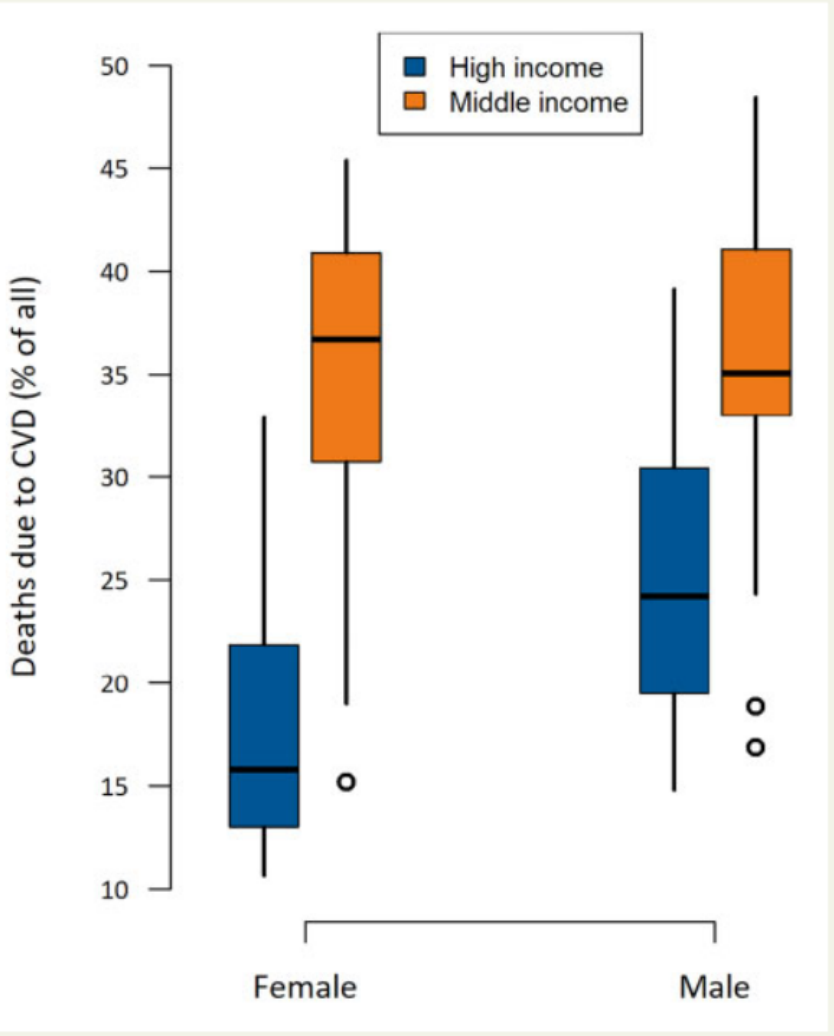


Figure 53 Proportion of all premature deaths (<70 years old) caused by cardiovascular diseases in ESC member countries by sex and national income status (latest year available). *Data source:*

Risk factors for atherothrombosis

Prevalence of obesity is increasing

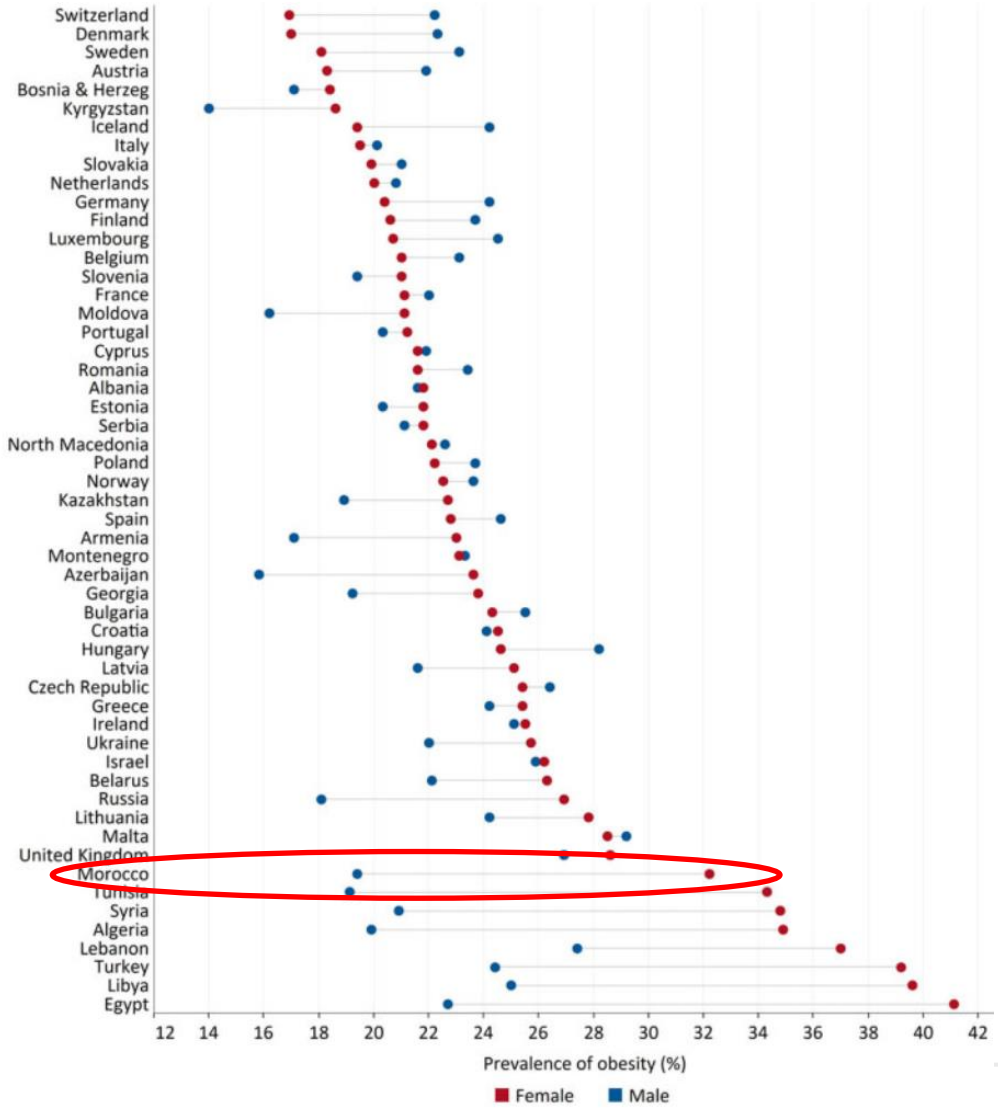


Figure 15 Prevalence of obesity (≥30 kg/m^2) by sex among adults in ESC member countries (2016). *Data source*: WHO,

Women: 32 %
Men: 19 %

InterHeart case-control study

Very important case-control study of **Risk Factors** for acute myocardial infarction, carried out in 52 countries, 5 continents, 15,152 cases and 14,820 controls.

Results: 9 factors predict 90% of acute myocardial infarctions in men and 94% in women:

-6 risk factors (dyslipidemia with increased apoB/apoA1, smoking, high blood pressure, diabetes, abdominal obesity and psychosocial stress)

-3 protective factors (daily consumption of fruits and vegetables, regular alcohol consumption, regular physical exercise).

the INTERHEART case-control study. Lancet, 2004, 364, 937-952

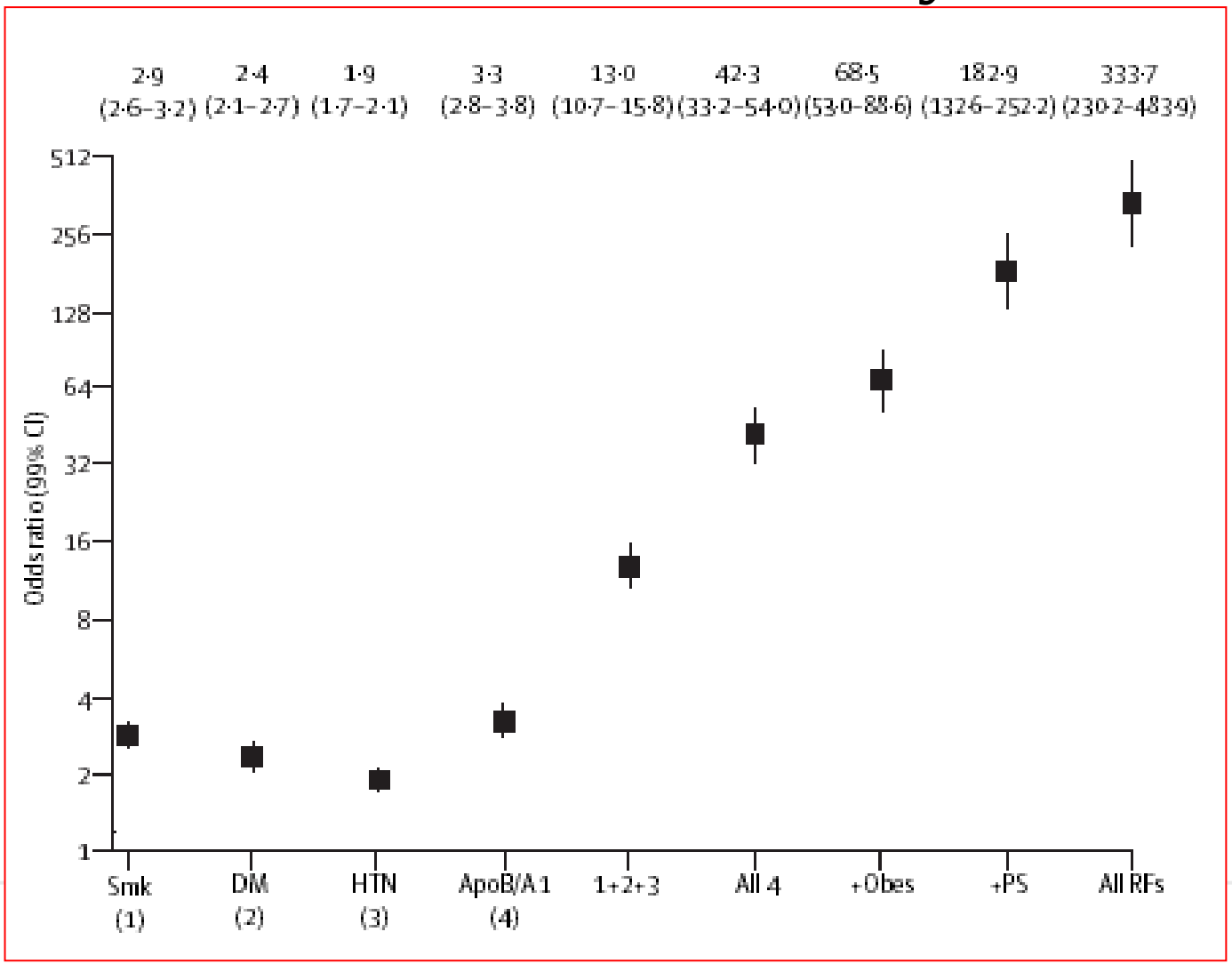
InterHeart

Universally true in all parts of the world, for all ages and both sexes

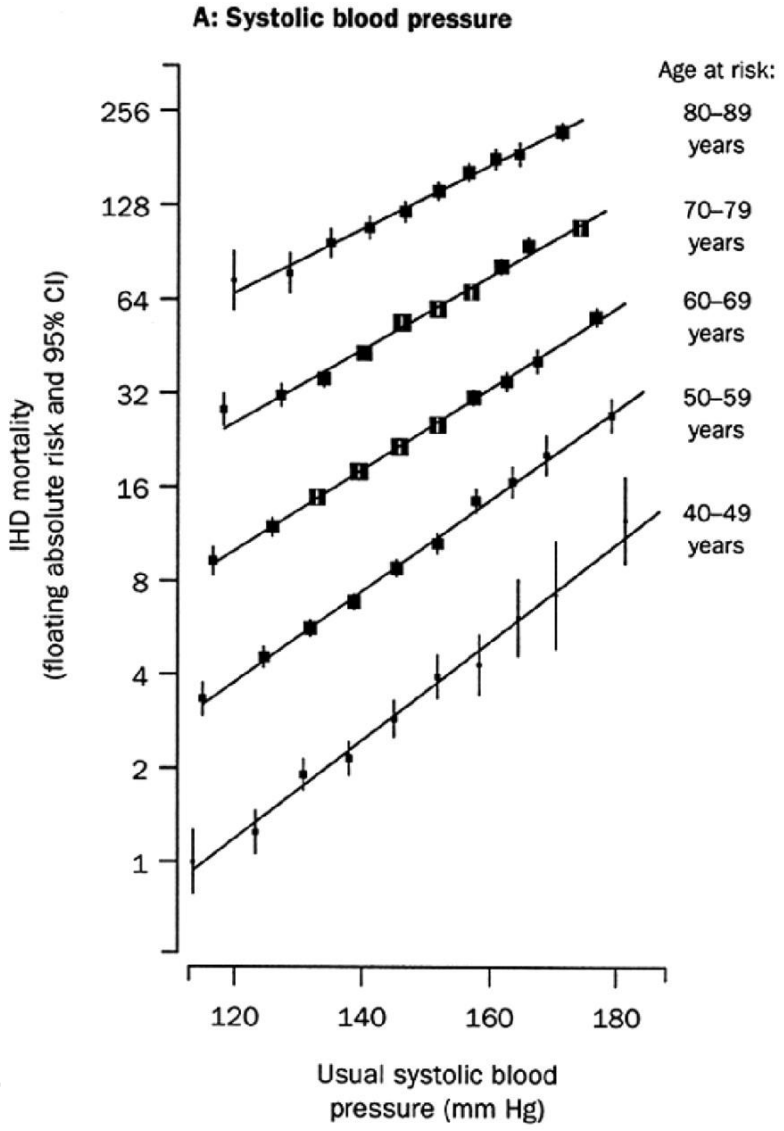
	Prevalence		Odds ratio (99% CI) adjusted for age, sex, and smoking (OR 1)
	Controls (%)	Cases (%)	
Risk factor			
Current smoking*	26·76	45·17	2·95 (2·72–3·20)
Current and former smoking*	48·12	65·19	2·27 (2·11–2·44)
Diabetes	7·52	18·45	3·08 (2·77–3·42)
Hypertension	21·91	39·02	2·48 (2·30–2·68)
Abdominal obesity (2 *vs* 1)†	33·40	30·21	1·36 (1·24–1·48)
Abdominal obesity (3 *vs* 1)†	33·32	46·31	2·24 (2·06–2·45)
All psychosocial‡	–	–	2·51 (2·15–2·93)
Vegetables and fruit daily*	42·36	35·79	0·70 (0·64–0·77)
Exercise*	19·28	14·27	0·72 (0·65–0·79)
Alcohol intake*	24·45	24·01	0·79 (0·73–0·86)
ApoB/ApoA1 ratio (2 *vs* 1)§	19·99	14·26	1·47 (1·28–1·68)
ApoB/ApoA1 ratio (3 *vs* 1)§	20·02	18·05	2·00 (1·74–2·29)
ApoB/ApoA1 ratio (4 *vs* 1)§	19·99	24·22	2·72 (2·38–3·10)
ApoB/ApoA1 ratio (5 *vs* 1)§	20·00	33-49	3·87 (3·39–4·42)
All above risk factors combined¶	–	–	129·20 (90·24–184·99)

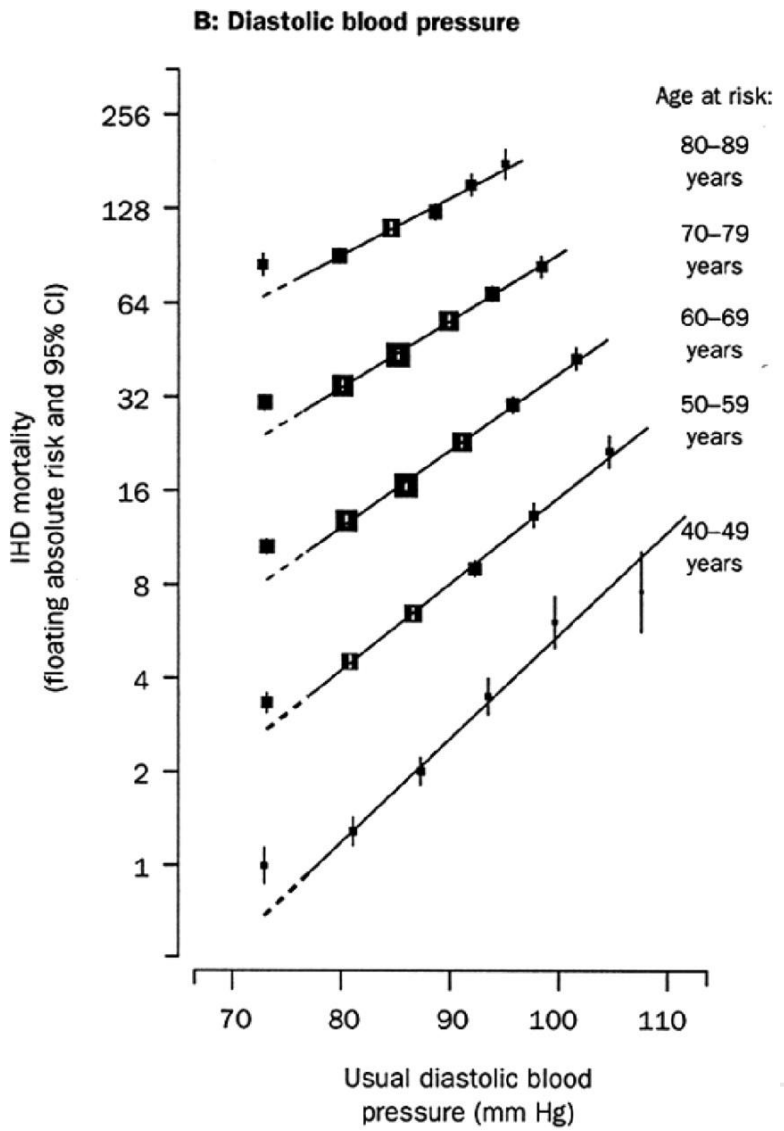
Synergistic effects of risk factors

The Interheart Study



Coronary artery disease (CHD) mortality for each decade of age as a function of BP at the beginning of the decade





Chobanian, A. V. et al. Hypertension 2003;42:1206-1252

Hypertension is the major risk factor for CVD

A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010

Stephen S Lim‡, Theo Vos, Abraham D Flaxman, Goodarz Danaei, Kenji Shibuya, Heather Adair-Rohani*, Markus Amann*, H Ross Anderson*,

Compared to the normotensive population, hypertension multiplies the relative risk of cardiovascular events:

- ✓ **Stroke (× 7)**
- ✓ **Heart failure (× 4)**
- ✓ **Coronary insufficiency (× 3)**
- ✓ **Arterial disease of the lower extremities (× 2)**

	Disability-adjusted life-years (%)
Physiological risk factors	
High blood pressure	53%
High total cholesterol	29%
High body-mass index	23%
High fasting plasma glucose	16%
Alcohol use	33%
Tobacco smoking, including second-hand smoke	31%
Dietary risk factors and physical inactivity	
Diet low in nuts and seeds	40%
Physical inactivity and low physical activity	31%
Diet low in fruits	30%
Diet low in seafood omega-3 fatty acids	22%
Diet low in whole grains	17%
Diet high in sodium	17%
Diet high in processed meat	13%
Diet low in vegetables	12%
Diet low in fibre	11%
Diet low in polyunsaturated fatty acids	9%
Diet high in trans fatty acids	9%
Diet high in sugar-sweetened beverages	2%
Air pollution	
Ambient particulate matter pollution	22%
Household air pollution from solid fuels	18%
Other environmental risks	
Lead exposure	4%

Table 2: Proportion of ischaemic heart disease disability-adjusted life-years attributable to individual risk factors, worldwide, 2010

Lancet 2012;380:2224-2260

Hypertension is a risk factor

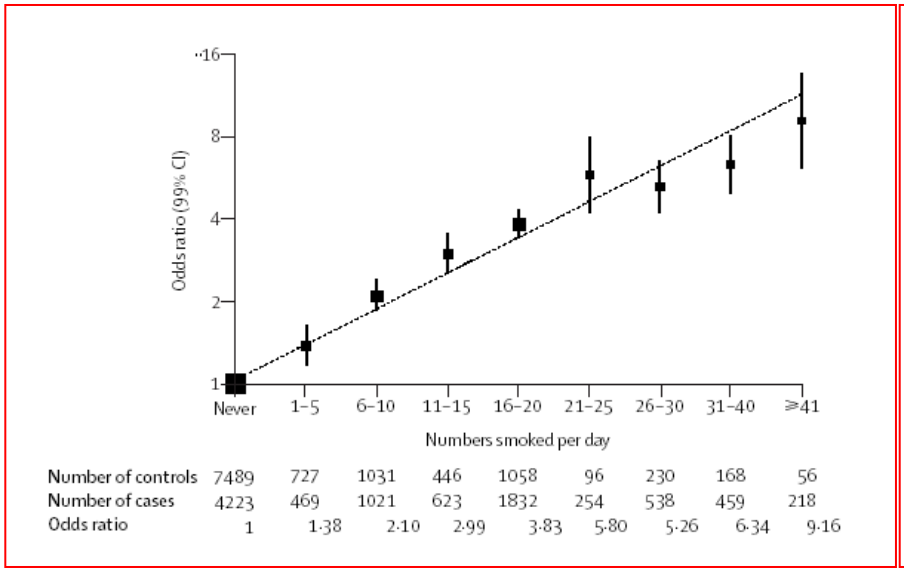
A variable is a **risk factor** if it is present before the outcome is observed and if it is significantly associated with the outcome

Key elements of a risk factor:
(1) the risk factor precedes the outcome in time;
(2) a person WITH a risk factor has a higher risk compared to a randomly selected person from the population
(3) the relationship between a risk factor and an outcome is probabilistic, not deterministic.

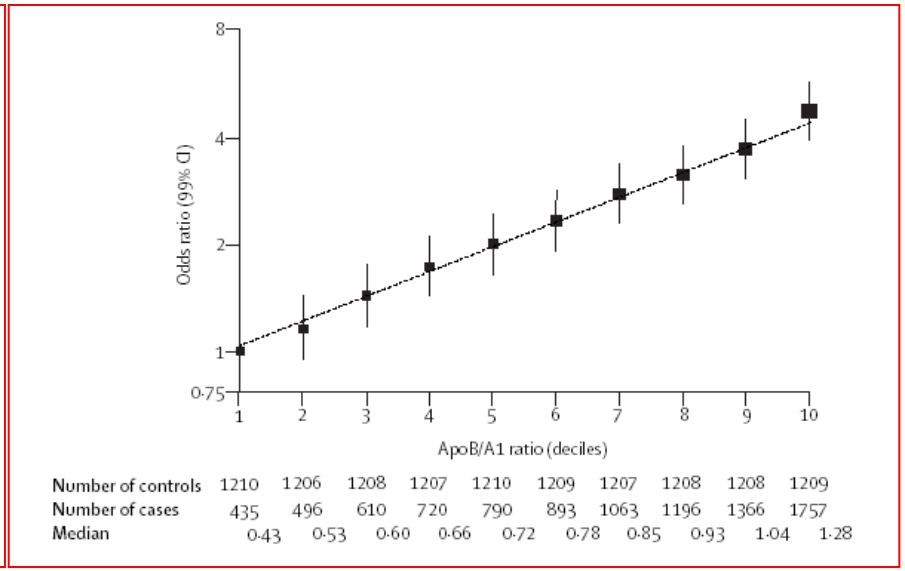
There is an ongoing relationship between systolic AND diastolic BP and the risk of cardiovascular complications

InterHeart Study

Smoking and Dyslipidemia are also clear RF



Number of controls	7489	727	1031	446	1058	96	230	168	56
Number of cases	4223	469	1021	623	1832	254	538	459	218
Odds ratio	1	1·38	2·10	2·99	3·83	5·80	5·26	6·34	9·16

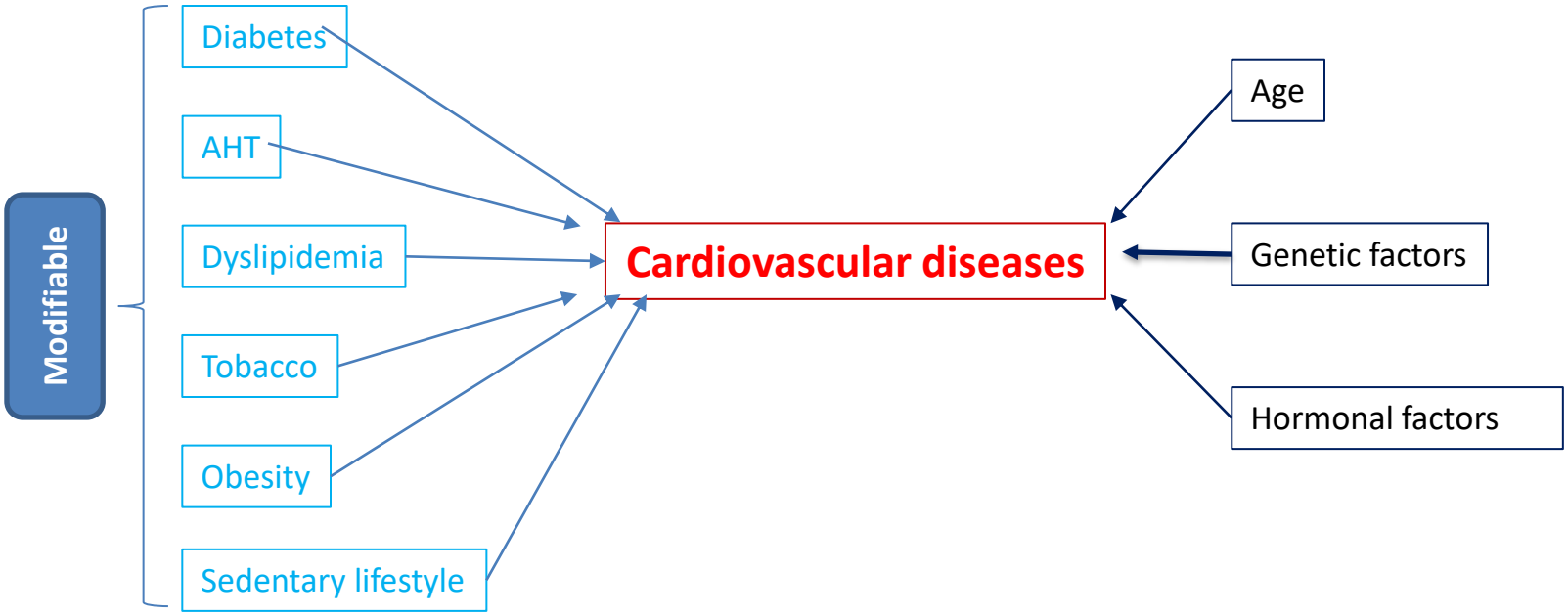


Number of controls	1210	1206	1208	1207	1210	1209	1207	1208	1208	1209
Number of cases	435	496	610	720	790	893	1063	1196	1366	1757
Median	0·43	0·53	0·60	0·66	0·72	0·78	0·85	0·93	1·04	1·28

- a clinical element whose presence statistically increases CV morbidity and mortality.

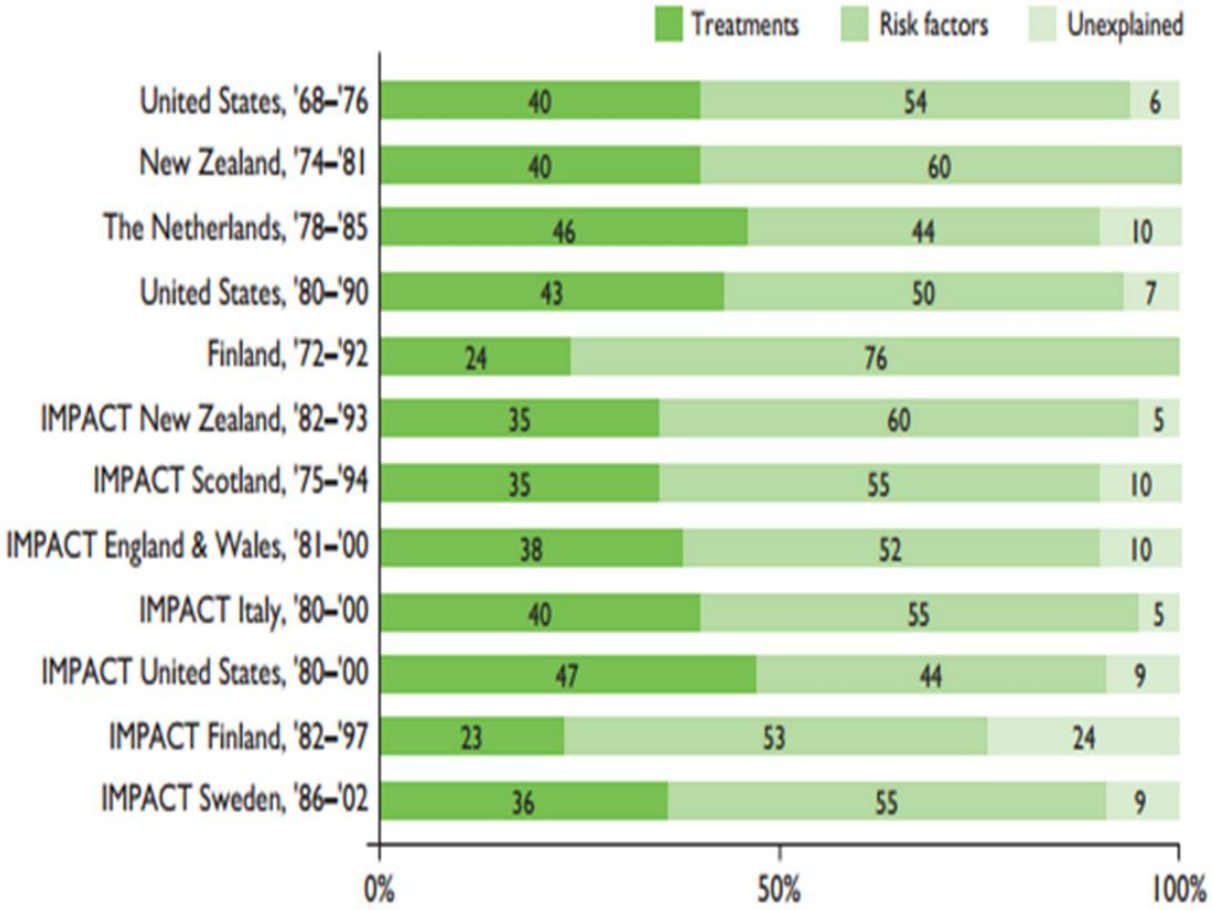
the INTERHEART case-control study. Lancet, 2004, 364, 937-952

Prevention of Cardiovascular Diseases



PREVENTION = All actions carried out at the public or individual level aimed at eradicating, eliminating or minimizing the impact of Cardiovascular Diseases (CVD)

Important benefit of taking care of risk factors



- >50% of the observed reduction in mortality
- ~40% related to therapeutic progress

Air pollution

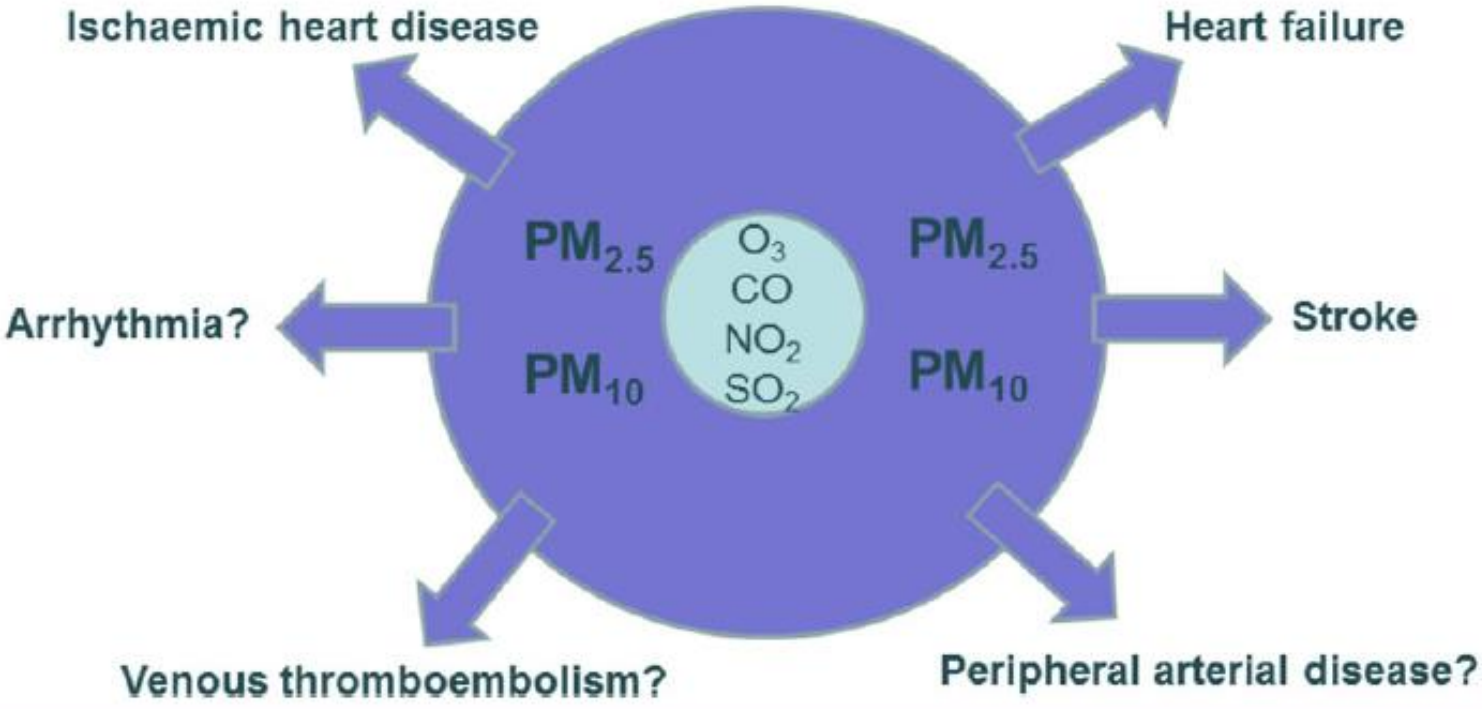


Figure 3 Established and unsettled clinical outcomes related to air pollution (gaseous and particulate).

European Heart Journal (2015) 36, 83–93 doi:10.1093/eurheartj/ehu458

Air pollution

✓ ***The main pollutants:***

- ***Gaseous pollutants:***

Ozone, sulphur dioxide, nitrogen dioxide, carbon monoxide, benzene.

- ***Particulate matter+++: c***lassified according to their diameters into:

1) Respirable particles (PM10): enter the bronchi (ø < 10 µm)

2) Fine particulate matter (PM2.5): penetrate the cells (ø < 2.5 µm)

3) Ultrafine particles (PM1): pass the alveola-capillary barrier (ø < 1 µm)

Air pollution

- *The Great Smog of London 1952*
- *12000 deaths (3000-5000 cardiovascular deaths)*

doi:10.1093/eurheartj/ehw622

Air pollution and myocardial infarction

Air pollution is associated with increased risk of myocardial infarction (MI) despite 'safe' levels according to an ESC Congress (London) presentation

Particulate matter and NO_2 air pollution are associated with increased risk of severe MIs despite being within European recommended levels, according to research presented at ESC Congress by Dr Jean-Francois Argacha MD PhD, a cardiologist at University Hospital Brussels (UZ Brussel-Vrije Universiteit Brussel), in Belgium.

'Dramatic health consequences of air pollution were first described in Belgium in 1930 after the Meuse Valley fog', said Dr Argacha. 'Nowadays, the World Health Organization (WHO) considers air pollution as one of the largest avoidable causes of mortality. Besides the pulmonary and carcinogenic effects of air pollution, exposure to air pollution has been associated with an increased risk in cardiovascular mortality.'

Meuse Valley Fog Dec 1930

The current study investigated the effect of short term exposure to air pollution on the risk of ST-segment elevation myocardial infarction (STEMI).

Ambient air pollution is a mixture of particulate matter (PM) and gaseous pollutants such as sulphur dioxide (SO_2), nitric dioxide (NO_2), and ozone (O_3). Fine particle pollution, also called PM2.5 (less than 2.5μm

Between 2009 and 2013, there were 11 428 hospitalizations for STEMI. The researchers found that 10 μg/m^3 increases in ambient PM2.5 concentrations were associated with a 2.8% increase in STEMI while 10 μg/m^3 rises in NO_2 were associated with a 5.1% increased risk (*Figure 1*). These associations were only observed in men.

'The association between STEMI and air pollution was observed within one day of exposure', said Dr Argacha. 'This was despite the fact that concentrations of air pollutants were within the European air quality

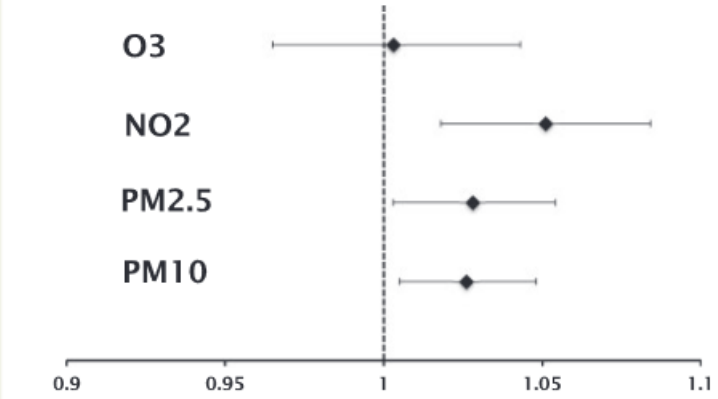


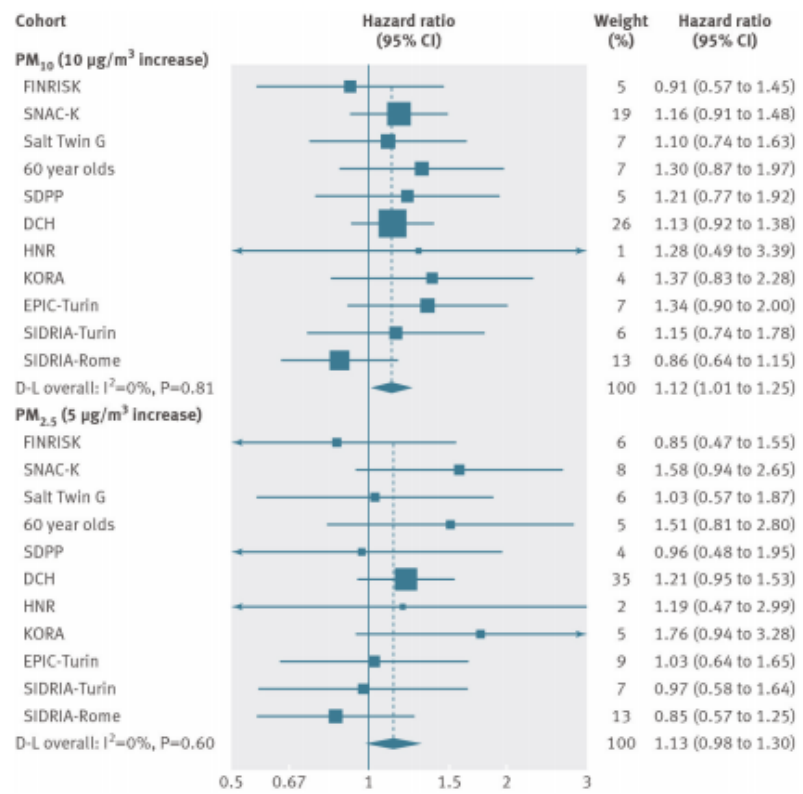
Figure 1 Odds ratio of STEMI for each 10 μg/m^3 rise in air pollutant.

Air pollution

BMJ 2014;348:f7412 doi: 10.1136/bmj.f7412 (Published 21 January 2014)

RES

Long term exposure to ambient air pollution incidence of acute coronary events: prospecti study and meta-analysis in 11 European coh the ESCAPE Project



100,000 people
11 European sites
2000-2007
Follow-up 11.5 years

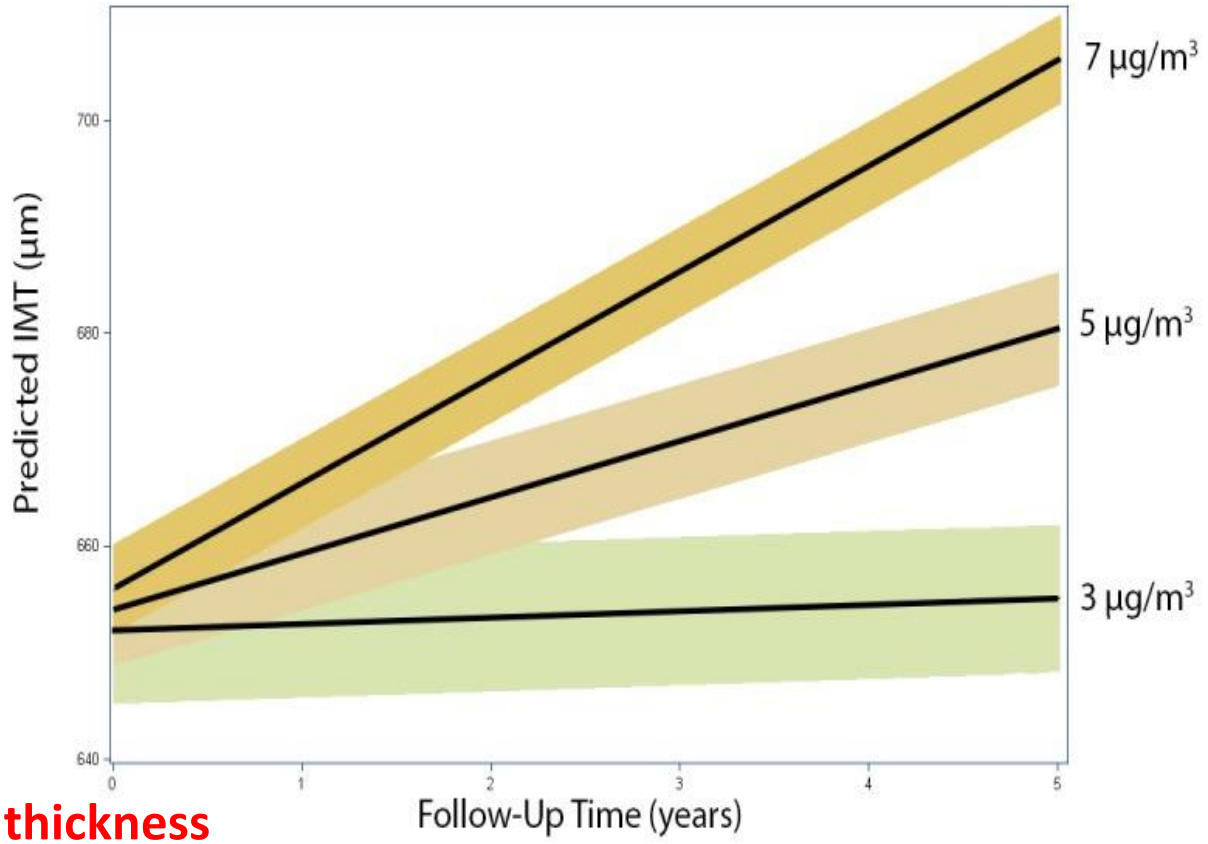
+10 µg/m³ PM10 = +13% coronary events
+5 µg/m³ PM2.5 = +12% coronary events

Air pollution

Fine Particulate Air Pollution and the Progression of Carotid Intima-Medial Thickness: A Prospective Cohort Study from the Multi-Ethnic Study of Atherosclerosis and Air Pollution

Sara D. Adar[1,2*], Lianne Sheppard[2,3], Sverre Roux[1], Matthew Budoff[6,7], David R. Jacobs,

5660 people
2000-2005
Multiple cities in the USA



+2.5 µg/m³ PM2.5

=

+0.5 µm/year intima-media thickness

Air pollution

Global association of air pollution and heart failure: a systematic review and meta-

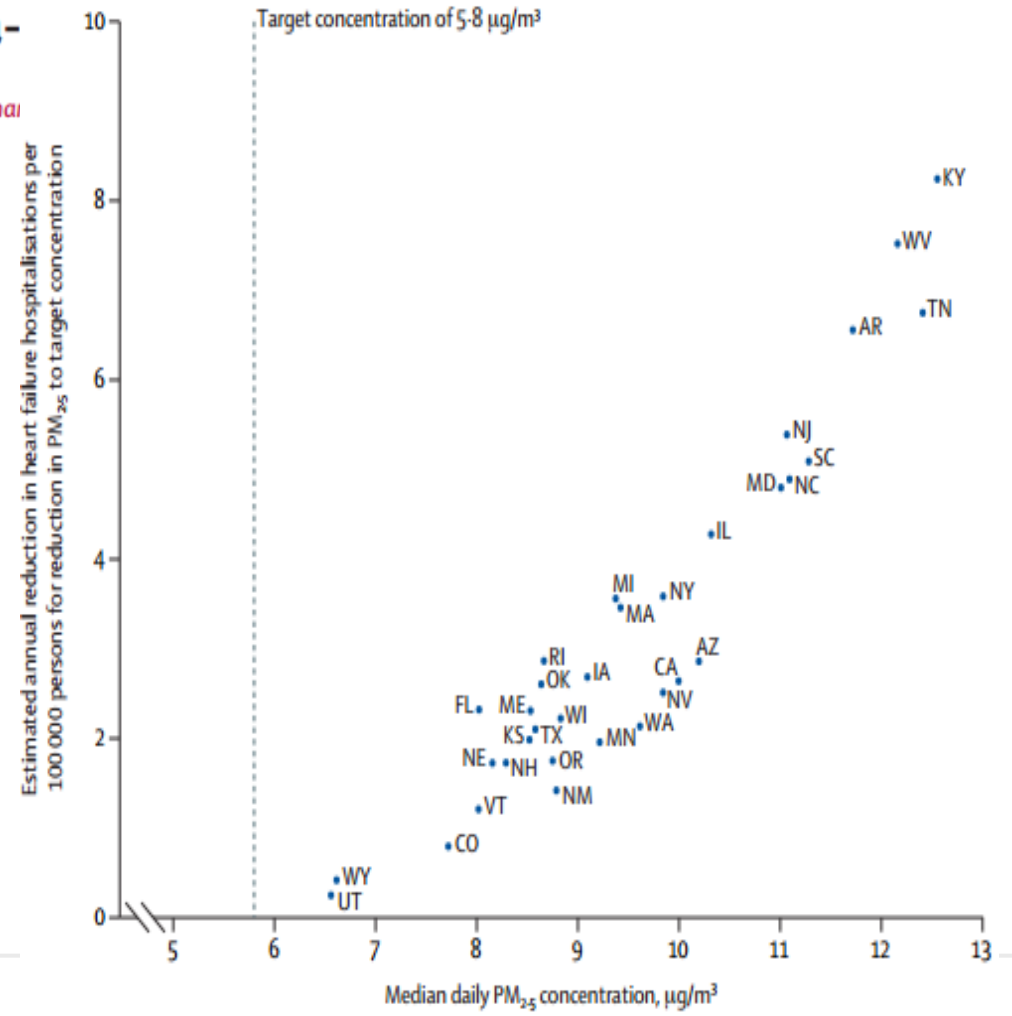
Anoop S V Shah, Jeremy P Langrish, Harish Nair, David A McAllister, Amar

Meta-analysis of 35 studies

Table 2 **Short-term association between gaseous and particulate air pollutants and hospitalization or mortality related to heart failure**

	Number of events	% Increase in risk (95% CI)
Gaseous pollutants		
Carbon monoxide (per 1 ppm)	1 969 500	3.52 (2.52–4.54)
Sulphur dioxide (per 10 ppb)	771 471	2.36 (1.35–3.38)
Nitrogen dioxide (per 10 ppb)	916 668	1.70 (1.25–2.16)
Ozone (per 10 ppb)	887 531	0.46 (−0.10–1.02)
Particulate pollutants		
$PM_{2.5}$ (per 10 μg/m^3)	1 520 099	2.12 (1.42–2.82)
PM_{10} (per 10 μg/m^3)	896 889	1.63 (1.20–2.07)

Ppm, parts per million; Ppb, parts per billion. Modified from Shah *et al.*[47]



Air pollution

✓ Epidemiology:

- *3.1 million deaths in 2010**
- *Ninth modifiable factor of cardiovascular risk (ahead of sedentary lifestyle, high-salt diet, isolated elevation of total cholesterol).*
- *0.8% increase in short-term cardiovascular mortality***.*
- *11% increase in long-term cardiovascular mortality****.*

*A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2224–2260)

**Atkinson RW, Kang S, Anderson HR, Mills IC, Walton HA. Epidemiological time series studies of PM2.5 and daily mortality and hospital admissions: a systematic review and meta-analysis. Thorax 2014;69:660–665

***Hoek G, Krishnan RM, Beelen R, Peters A, Ostro B, Brunekreef B, Kaufman JD. Longterm air pollution exposure and cardio-respiratory mortality: a review. Environ Health 2013;12:43.

New recommendations (13)

Recommendations	Class
Policy interventions at the population level	
Putting in place measures to reduce air pollution, including reducing PM emission and gaseous pollutants, reducing the use of fossil fuels, and limiting carbon dioxide emissions, are recommended to reduce CVD mortality and morbidity.	I

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (1)

EAS ESC European Society of Cardiology

Task Force Members:

François Mach (ESC Chairperson) (Switzerland), Colin Baigent (ESC Chaiperson) (United Kingdom), Alberico L. Catapano (EAS Chairperson) (Italy), Konstantinos C. Koskinas (Switzerland), Manuela Casula[1] (Italy), Lina Badimon (Spain), M. John Chapman[1] (France), Guy G. De Backer (Belgium), Victoria Delgado (Netherlands), Brian A. Ference (United Kingdom), Ian M. Graham (Ireland), Alison Halliday (United Kingdom), Ulf Landmesser (Germany), Borislava Mihaylova (United Kingdom), Terje R. Pedersen (Norway), Gabriele Riccardi[1] (Italy), Dimitrios J. Richter (Greece), Marc S. Sabatine (United States of America), Marja-Riitta Taskinen[1] (Finland), Lale Tokgozoglu[1] (Turkey), Olov Wiklund[1] (Sweden).

[1]Representing the European Athero

www.escardio.org/guidelines

2021 ESC Guidelines on cardiovascular disease prevention in clinical practice

ESC

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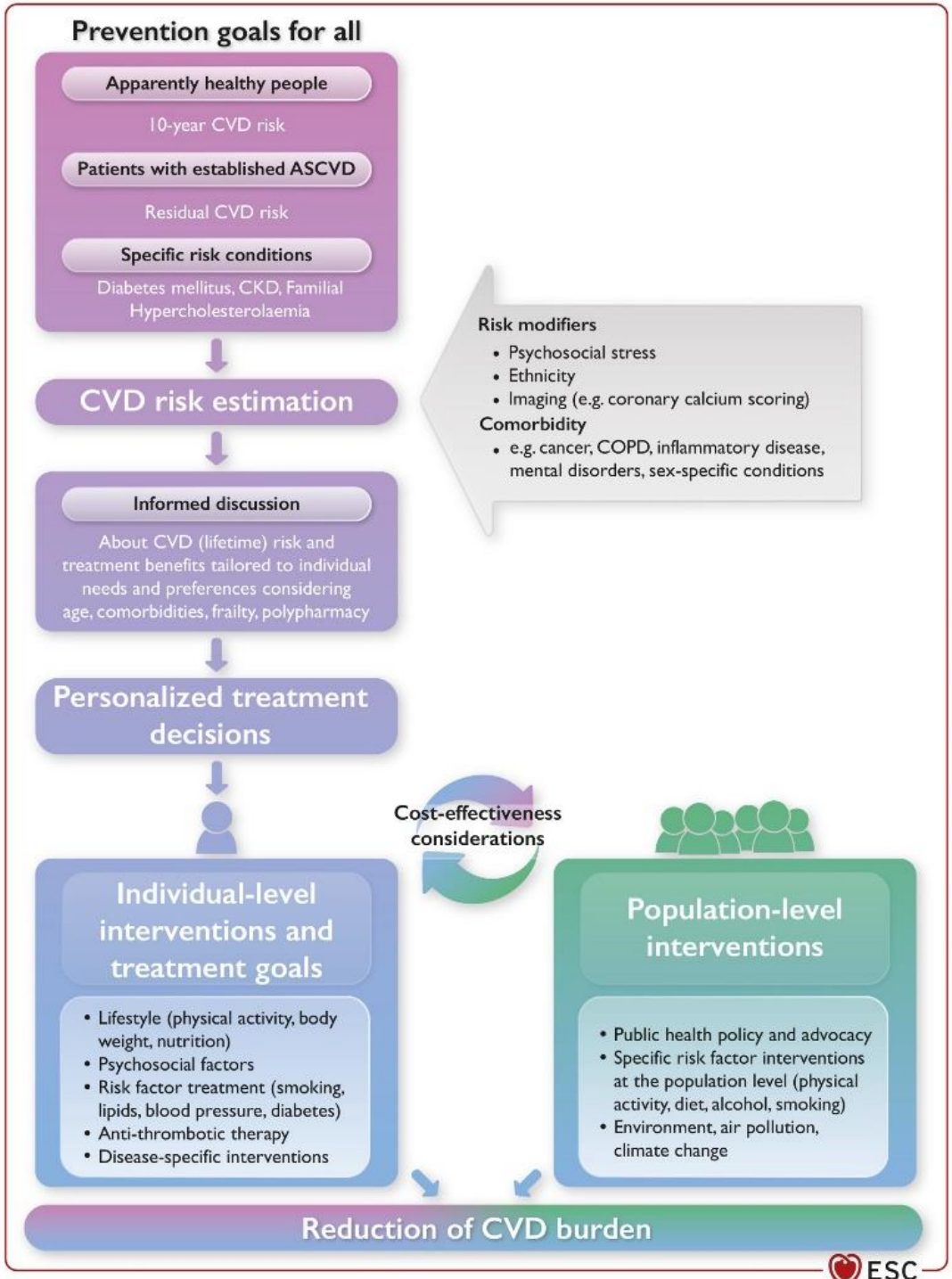
Prevention of CVD



SCORE2 risk prediction algorithms

1. Model development

Sex-specific, competing risk-adjusted risk models derived in 45 prospective cohorts in 13 countries (~680,000 individuals, and ~30,000 CVD events)

↓

Recalibration to four risk regions in Europe using age-, sex-, and region-specific risk factor values and CVD incidence rates (derived using data on ~10.8 million individuals)

↓

2. Model validation

External validation in 25 prospective cohorts in 15 European countries (~1.1 million individuals, and ~43,000 CVD events)

↓

C-indices ranged from 0.67 (95% confidence interval [CI] 0.65-0.68) to 0.81 (95% CI 0.76-0.86)

SCORE2 risk prediction algorithms key features

- Sex-specific risk prediction models
- Estimate 10-year risk of fatal and non-fatal CVD
- Calibrated to the most contemporary and representative CVD rates
- Available for four distinct European risk regions
- Can be rapidly updated to reflect future CVD incidence and risk factor profiles

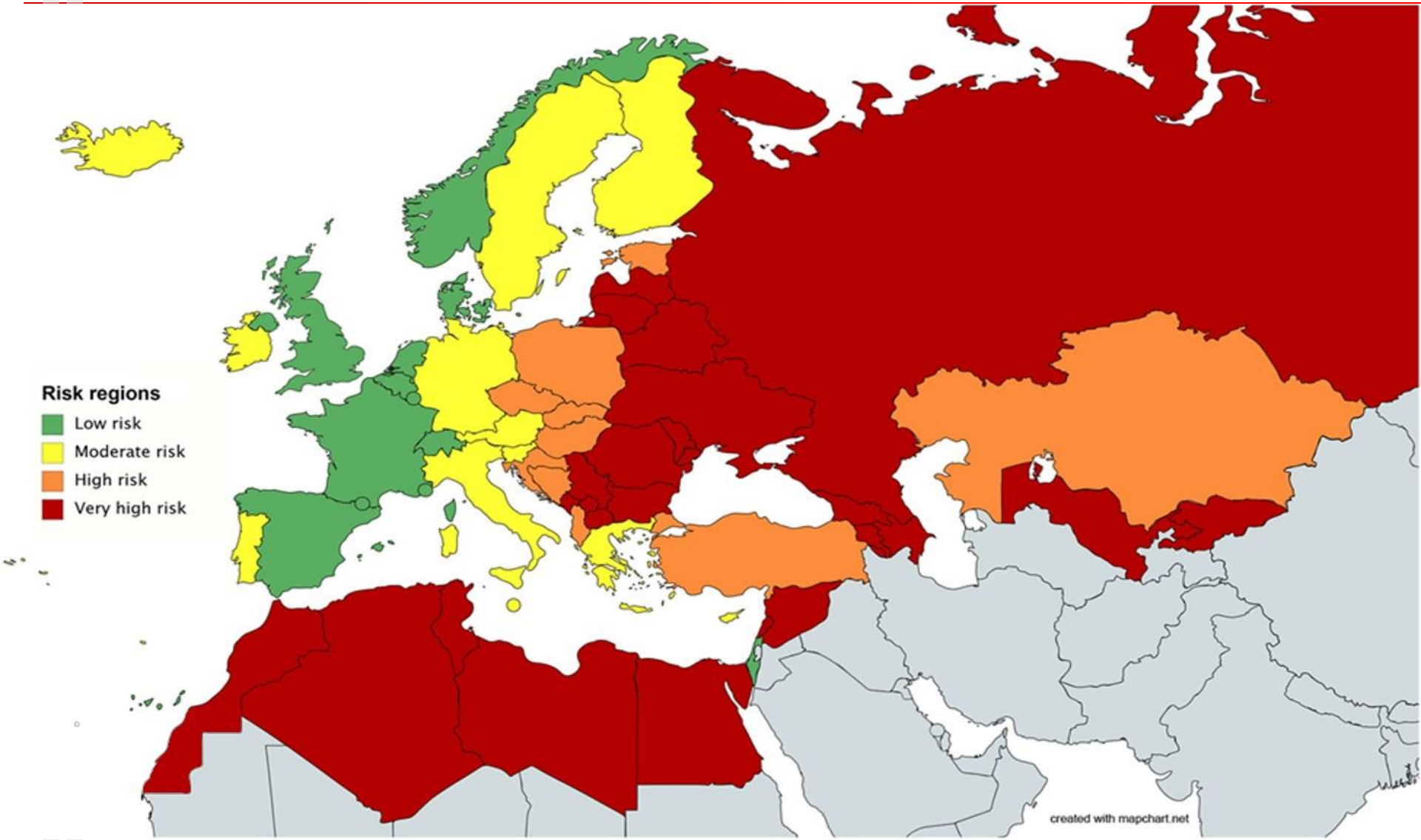
Individual example

Patient risk factors:
50 years old
Smoker
SBP: 140 mmHg
Cholesterol: 5.5 mmol/L
HDL-c: 1.3 mmol/L

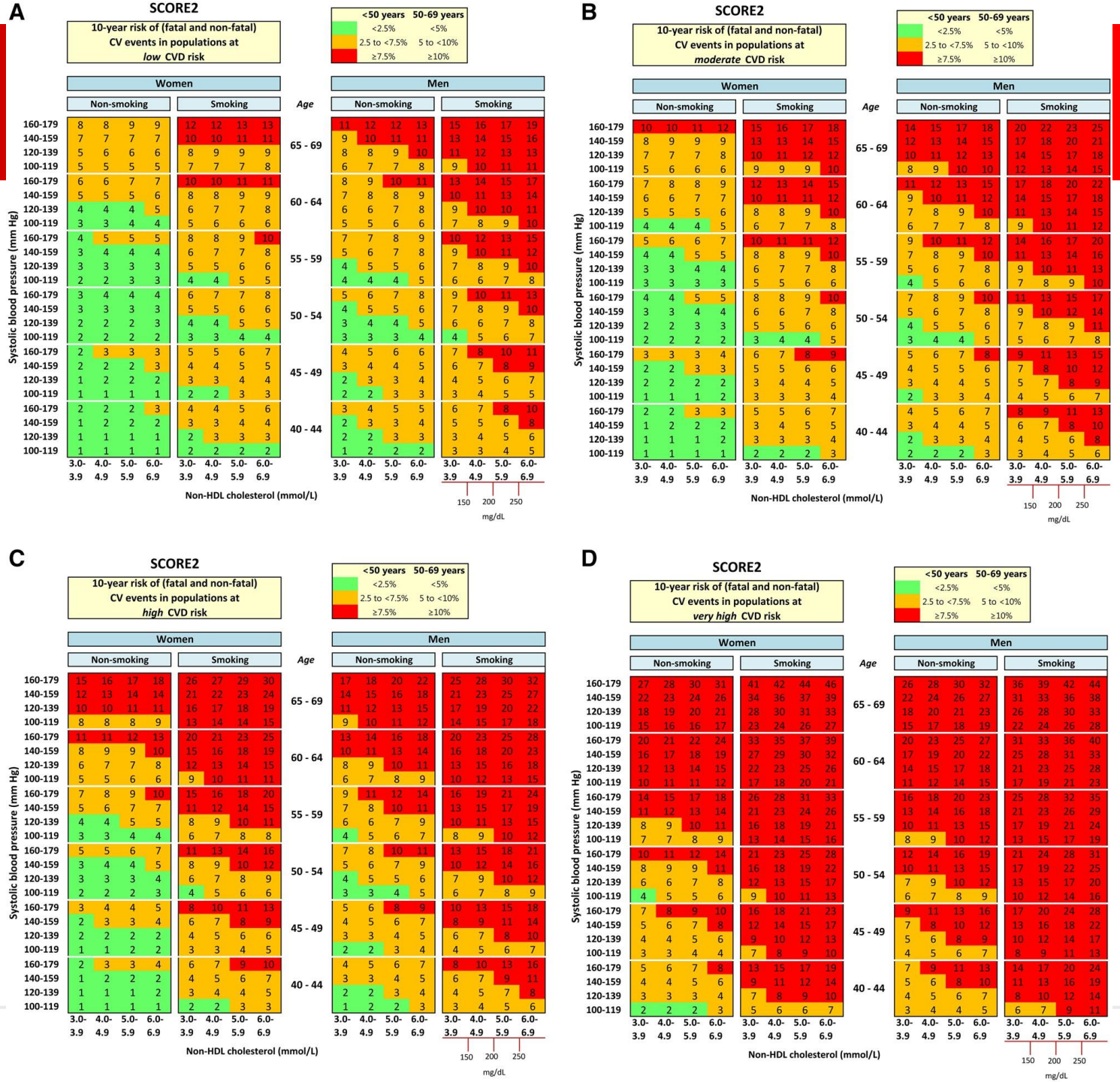
10-year risk depending on risk region

Low risk	Moderate risk	High risk	Very high risk	Low risk	Moderate risk	High risk	Very high risk
4.2%	5.1%	6.9%	13.7%	5.9%	7.5%	8.1%	14.0%

Eur Heart J, Volume 42, Issue 25, 1 July 2021, Pages 2439–2454, https://doi.org/10.1093/eurheartj/ehab309



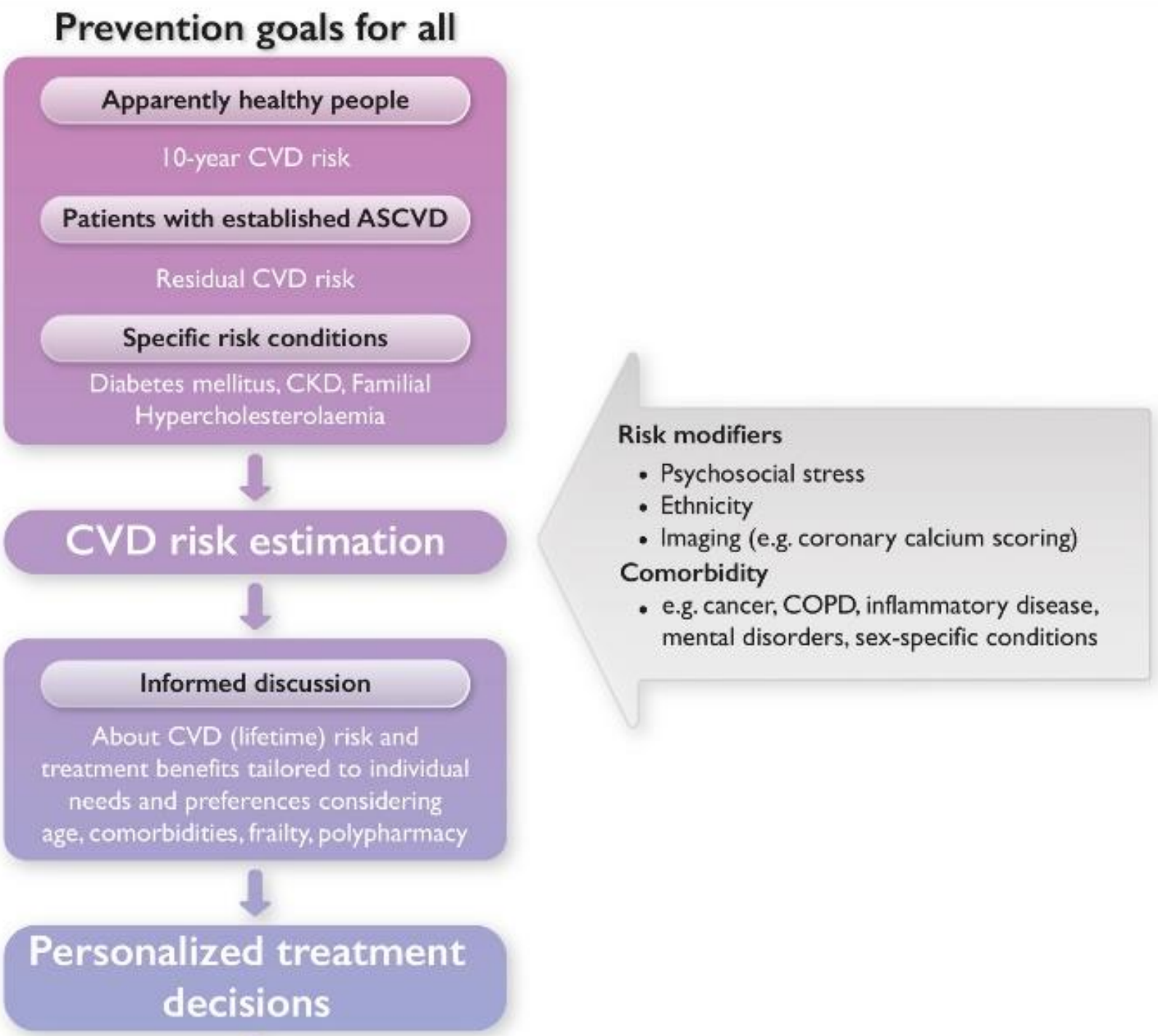
Countries were grouped into four risk regions according to their most recently reported WHO age- and sex-standardized overall CVD mortality rates per 100,000 population (ICD chapters 9, I00-I99). The four groupings were: low risk (<100 CVD deaths per 100,000), moderate risk (100 to <150 CVD deaths per 100,000), high risk (150 to <300 CVD deaths per 100,000), and very high risk (≥300 CVD deaths per 100,000)


A
SCORE2
10-year risk of (fatal and non-fatal) CV events in populations at low CVD risk
<50 years 50-69 years
<2.5% <5%
2.5 to <7.5% 5 to <10%
≥7.5% ≥10%
Women
Men
Non-smoking
Smoking
Age
65 - 69
60 - 64
55 - 59
50 - 54
45 - 49
40 - 44
160-179
140-159
120-139
100-119
Systolic blood pressure (mm Hg)
3.0-3.9
4.0-4.9
5.0-5.9
6.0-6.9
Non-HDL cholesterol (mmol/L)
150 200 250
mg/dL
B
SCORE2
10-year risk of (fatal and non-fatal) CV events in populations at moderate CVD risk
<50 years 50-69 years
<2.5% <5%
2.5 to <7.5% 5 to <10%
≥7.5% ≥10%
Women
Men
Non-smoking
Smoking
Age
65 - 69
60 - 64
55 - 59
50 - 54
45 - 49
40 - 44
160-179
140-159
120-139
100-119
Systolic blood pressure (mm Hg)
3.0-3.9
4.0-4.9
5.0-5.9
6.0-6.9
Non-HDL cholesterol (mmol/L)
150 200 250
mg/dL
C
SCORE2
10-year risk of (fatal and non-fatal) CV events in populations at high CVD risk
<50 years 50-69 years
<2.5% <5%
2.5 to <7.5% 5 to <10%
≥7.5% ≥10%
Women
Men
Non-smoking
Smoking
Age
65 - 69
60 - 64
55 - 59
50 - 54
45 - 49
40 - 44
160-179
140-159
120-139
100-119
Systolic blood pressure (mm Hg)
3.0-3.9
4.0-4.9
5.0-5.9
6.0-6.9
Non-HDL cholesterol (mmol/L)
150 200 250
mg/dL
D
SCORE2
10-year risk of (fatal and non-fatal) CV events in populations at very high CVD risk
<50 years 50-69 years
<2.5% <5%
2.5 to <7.5% 5 to <10%
≥7.5% ≥10%
Women
Men
Non-smoking
Smoking
Age
65 - 69
60 - 64
55 - 59
50 - 54
45 - 49
40 - 44
160-179
140-159
120-139
100-119
Systolic blood pressure (mm Hg)
3.0-3.9
4.0-4.9
5.0-5.9
6.0-6.9
Non-HDL cholesterol (mmol/L)
150 200 250
mg/dL

New recommendations (1)

Recommendations	Class
Risk factors and clinical conditions	
In apparently healthy people <70 years of age without established ASCVD, DM, CKD, genetic/rarer lipid or BP disorders, estimation of 10-year fatal and nonfatal CVD risk with SCORE2 is recommended.	I
In apparently healthy people ≥70 years of age without established ASCVD, DM, CKD, genetic/rarer lipid or BP disorder, estimation of 10-year fatal and nonfatal CVD risk with SCORE2-OP is recommended.	I
Patients with established ASCVD and/or DM and/or moderate-to-severe renal disease and/or genetic/rarer lipid or BP disorders are to be considered at high or very high CVD risk.	I

ASCVD: Atherosclerotic Cardiovascular DiseaseDM: Diabète mellitus
CKD: Chronic Kidney Disease
BP: Blood Pressure
OP: Old Person


Prevention goals for all
Apparently healthy people
10-year CVD risk
Patients with established ASCVD
Residual CVD risk
Specific risk conditions
Diabetes mellitus, CKD, Familial Hypercholesterolaemia
CVD risk estimation
Informed discussion
About CVD (lifetime) risk and treatment benefits tailored to individual needs and preferences considering age, comorbidities, frailty, polypharmacy
Personalized treatment decisions
Risk modifiers
Psychosocial stress
Ethnicity
Imaging (e.g. coronary calcium scoring)
Comorbidity
e.g. cancer, COPD, inflammatory disease, mental disorders, sex-specific conditions

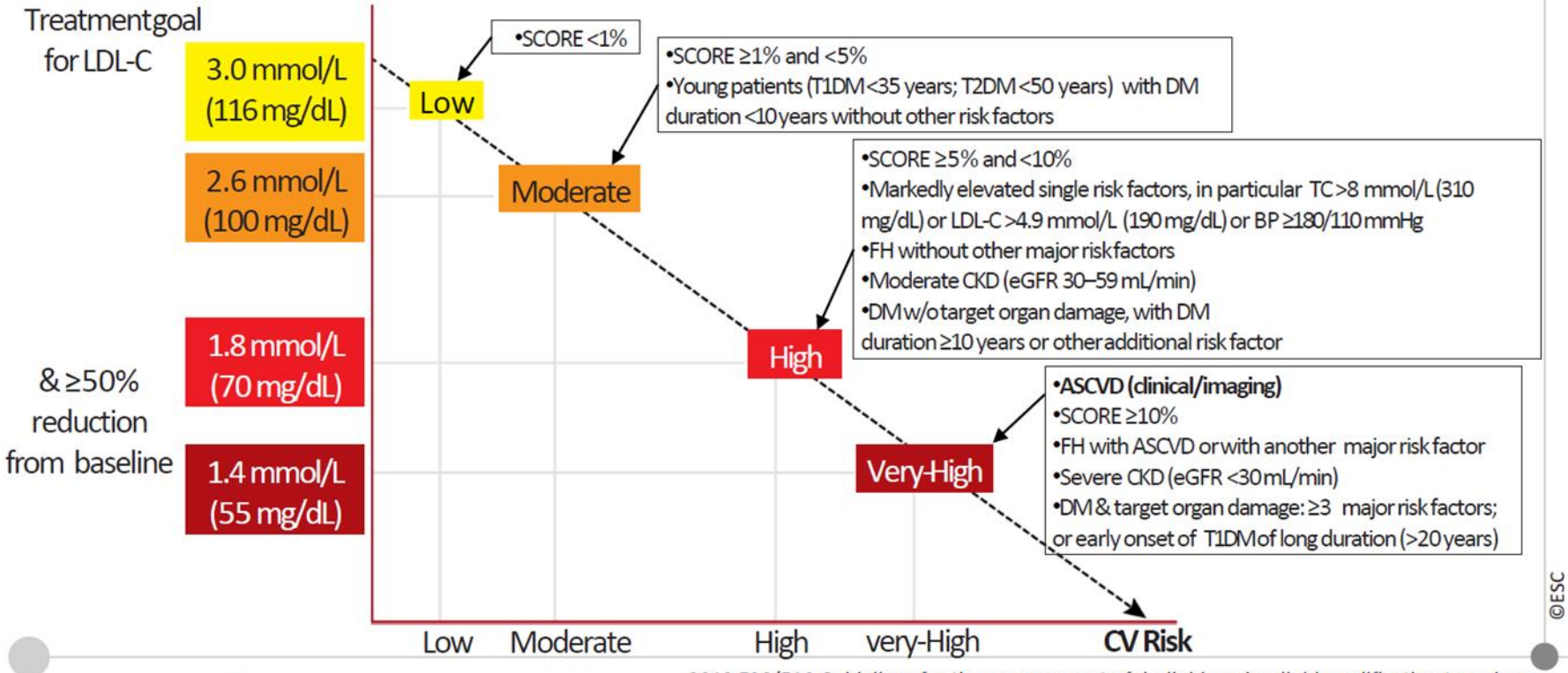
New recommendations (6)

Recommendations	Class
Risk factors and interventions at the individual level (continued)	
In patients with established ASCVD, lipid-lowering treatment with an ultimate LDL-C goal of <1.4 mmol/L (55 mg/dL) and a ≥50% reduction of LDL-C vs. baseline is recommended.	I
For secondary prevention patients not achieving their goals on a maximum tolerated dose of a statin and ezetimibe, combination therapy including a PCSK9 inhibitor is recommended.	I
In patients with type 2 DM at very high risk (e.g. with established ASCVD and/or severe TOD), intensive lipid-lowering therapy, ultimately aiming at ≥50% LDL-C reduction and an LDL-C of <1.4 mmol/L (<55 mg/dL) is recommended.	I
In patients with type 2 DM >40 years of age at high risk, lipid-lowering treatment with an ultimate LDL-C goal of ≥50% LDL-C reduction and an LDL-C of <1.8 mmol/L (70 mg/dL) is recommended.	I

2021 ESC Guidelines on cardiovascular disease prevention in clinical practice
(European Heart Journal 2021 – doi:10.1093/eurheartj/ehab484)

Treatment goals for low-density lipoprotein cholesterol (LDL-C) across categories of total cardiovascular disease risk

EAS ESC European Society of Cardiology



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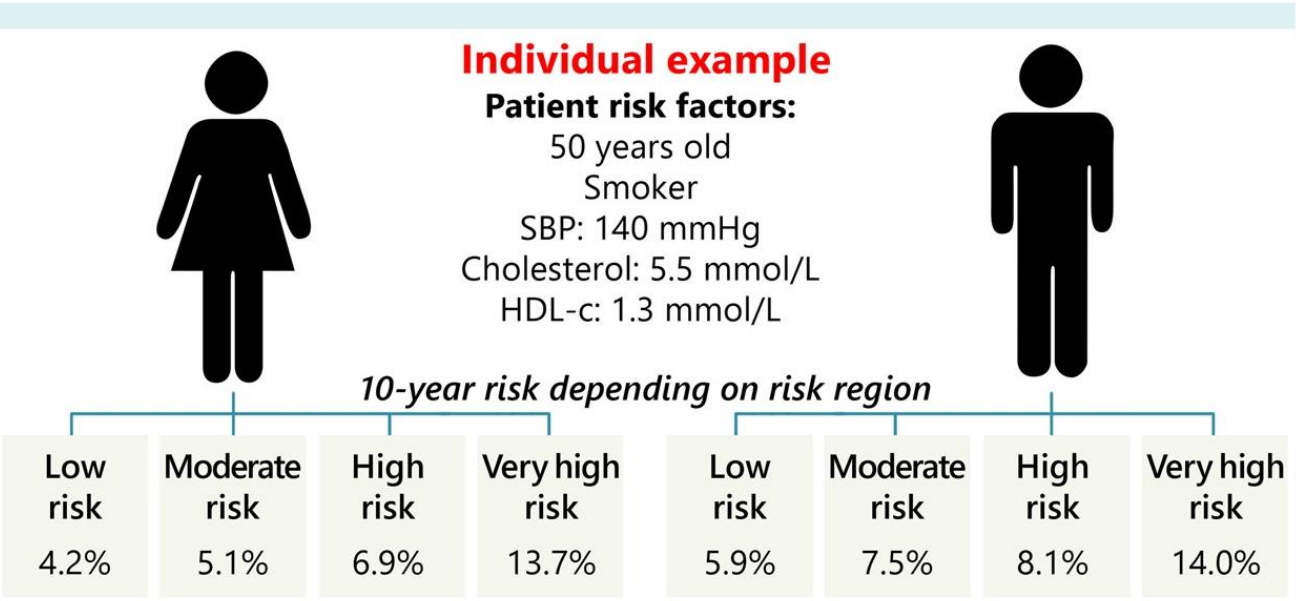
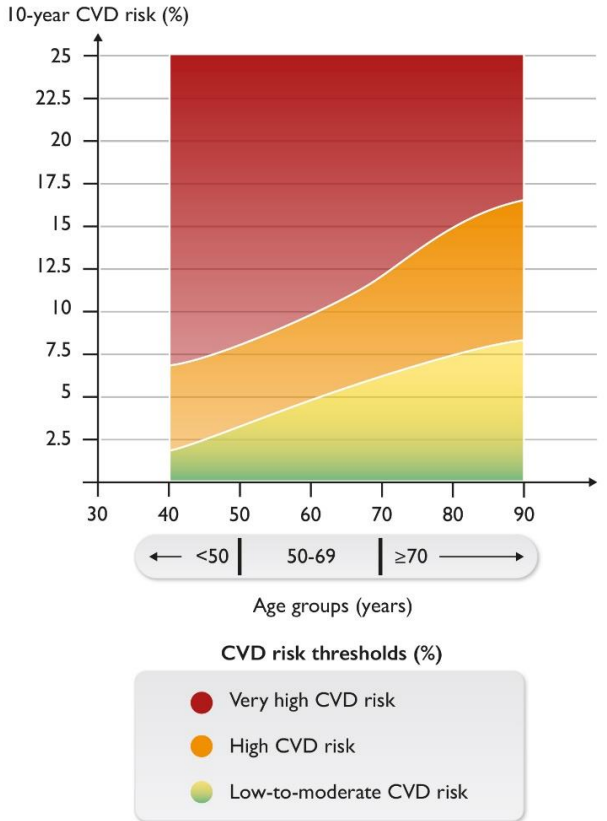
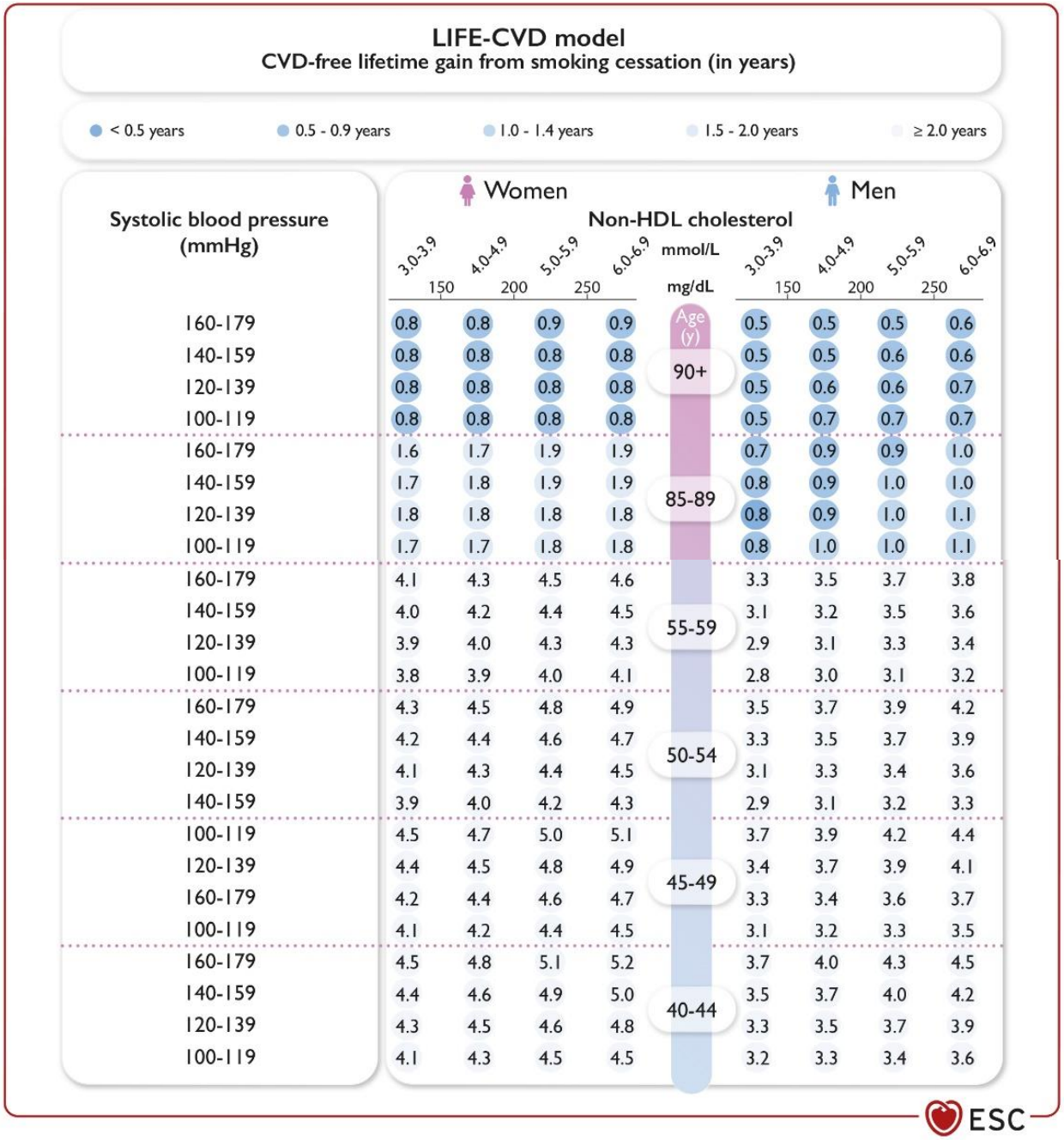
2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

Cardiovascular disease risk categories based on SCORE2 and SCORE2-OP in apparently healthy people according to age

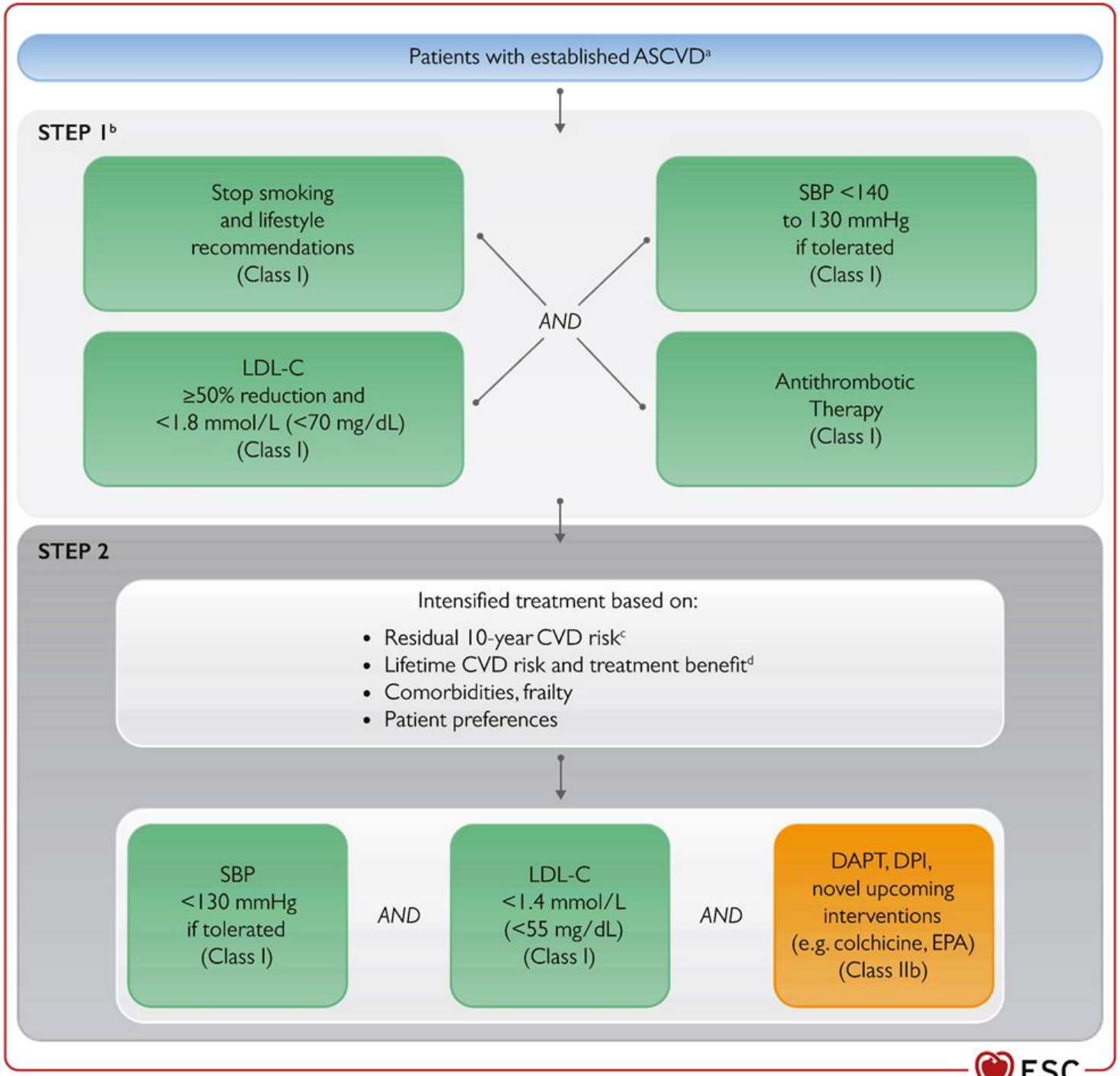
	<50 years	50-69 years	≥70 years[a]
Low-to-moderate CVD risk: risk factor treatment generally not recommended	<2.5%	<5%	<7.5%
High CVD risk: risk factor treatment should be considered	2.5 to <7.5%	5 to <10%	7.5 to <15%
Very high CVD risk: risk factor treatment generally recommended[a]	≥7.5%	≥10%	≥15%







Lifetime CVD benefit from smoking cessation for apparently healthy persons (1)


Patients with established ASCVD[a]
STEP 1[b]
Stop smoking and lifestyle recommendations (Class I)
SBP <140 to 130 mmHg if tolerated (Class I)
AND
LDL-C ≥50% reduction and <1.8 mmol/L (<70 mg/dL) (Class I)
Antithrombotic Therapy (Class I)
STEP 2
Intensified treatment based on:
• Residual 10-year CVD risk[c]
• Lifetime CVD risk and treatment benefit[d]
• Comorbidities, frailty
• Patient preferences
SBP <130 mmHg if tolerated (Class I)
AND
LDL-C <1.4 mmol/L (<55 mg/dL) (Class I)
AND
DAPT, DPI, novel upcoming interventions (e.g. colchicine, EPA) (Class IIb)

New recommendations (5)

Recommendations	Class
Risk factors and interventions at the individual level	
It is recommended to reduce sedentary time to engage in at least light activity throughout the day to reduce all-cause and CV mortality and morbidity.	I
It is recommended to adopt a Mediterranean or similar diet to lower risk of CVD.	I
It is recommended to restrict alcohol consumption to a maximum of 100 g per week.	I
It is recommended to eat fish, preferably fatty, at least once a week and restrict (processed) meat.	I
Patients with mental disorders need intensified attention and support to improve adherence to lifestyle changes and drug treatment.	I
Smoking cessation is recommended regardless of weight gain, as weight gain does not lessen the ASCVD benefits of cessation.	I

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Recommendations for physical activity (1)

Recommendations	Class	Level
It is recommended for adults of all ages to strive for at least 150–300 min a week of moderate-intensity or 75–150 min a week of vigorous-intensity aerobic PA, or an equivalent combination thereof, to reduce all-cause mortality, CV mortality, and morbidity.	I	A
It is recommended that adults who cannot perform 150 min of moderate-intensity PA a week should stay as active as their abilities and health condition allow.	I	B
It is recommended to reduce sedentary time to engage in at least light activity throughout the day to reduce all-cause and CV mortality and morbidity.	I	B

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Absolute intensity			Relative intensity		
Intensity	**MET[a]**	**Examples**	**%HR_{max}**	**RPE (Borg scale score)**	**Talk test**
Light	1.1–2.9	Walking <4.7 km/h, light household work	57–63	10–11	
Moderate	3–5.9	Walking at moderate or brisk pace (4.1–6.5 km/h), slow cycling (15 km/h), painting/decorating, vacuuming, gardening (mowing lawn), golf (pulling clubs in trolley), tennis (doubles), ballroom dancing, water aerobics	64–76	12–13	Breathing is faster but compatible with speaking full sentences
Vigorous	≥6	Race-walking, jogging or running, cycling >15 km/h, heavy gardening (continuous digging or hoeing), swimming laps, tennis (singles)	77–95	14–17	Breathing very hard, incompatible with carrying on a conversation comfortably

New recommendations (7)

Recommendations	Class
Risk factors and interventions at the individual level (continued)	
It is recommended that the first objective of treatment is to lower BP to <140/90 mmHg in all patients, and that subsequent BP targets are tailored to age and specific comorbidities.	I
In treated patients aged 18—69 years, it is recommended that SBP should ultimately be lowered to a target range of 120—130 mmHg in most patients.	I
In treated patients aged ≥70 years, it is recommended that SBP should generally be targeted to <140 and down to 130 mmHg if tolerated.	I
In all treated patients, DBP is recommended to be lowered to <80 mmHg.	I

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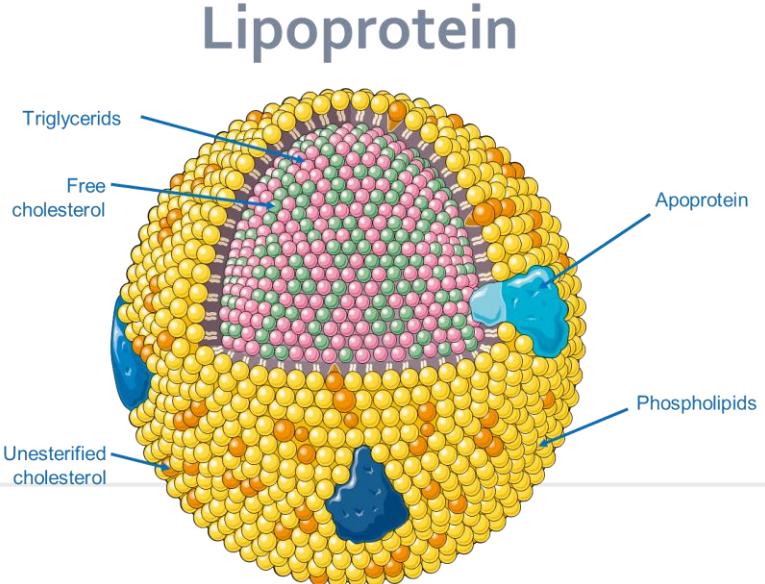
Dyslipidemia and atherogenesis

Genetic and environmental factors influence lipid metabolism.

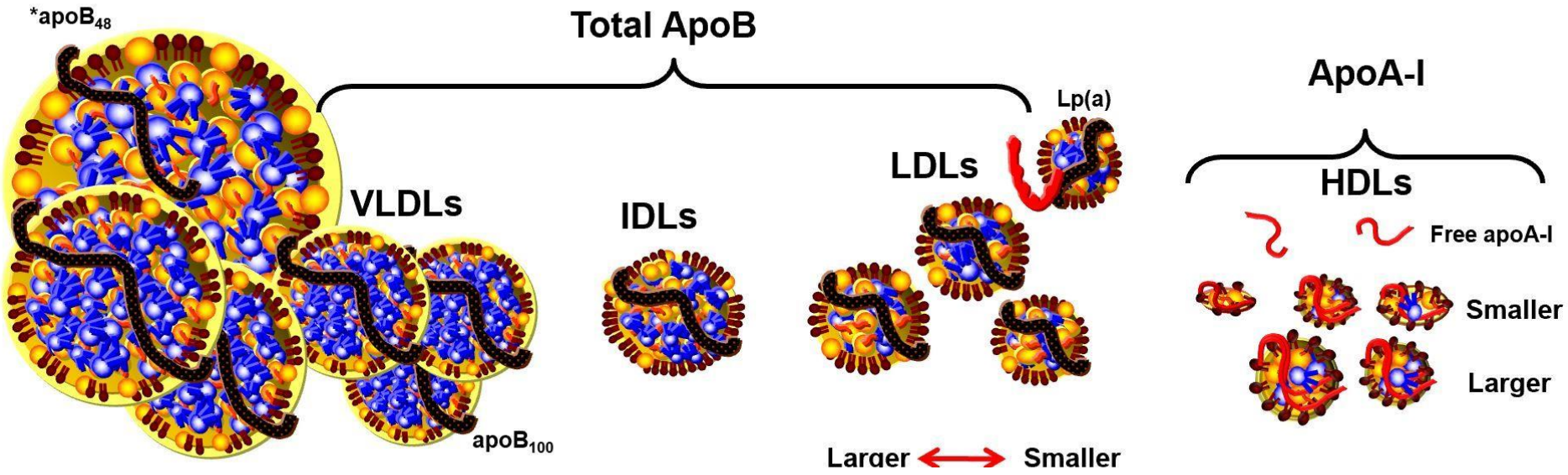
Their interactions lead to changes in lipoprotein levels and/or function → formation of atherosclerosis

Blood levels **↑ lipoproteins** are **considered risk factors for CVD**:
Total Cholesterol (**TC**)
Low-Density Lipoprotein-bound cholesterol (LDL-C)
Apoprotein B (**apo B**)
Non-HDL cholesterol (**non-HDL-C**)
Triglycerides (**TG**)
Lp (a)



Dyslipidemia and atherogenesis

Lipid and Lipoprotein metrics related to TG-rich Lipoproteins



Total apoB = chylo-apoB +VLDL-apoB +IDL-apoB + LDL-apoB +Lp(a)-apoB *Note chylo-apoB makes a negligible contribution

The actual TG concentration associated with TG-rich lipoproteins is extremely variable and starts ~ 100-130 mg/dL

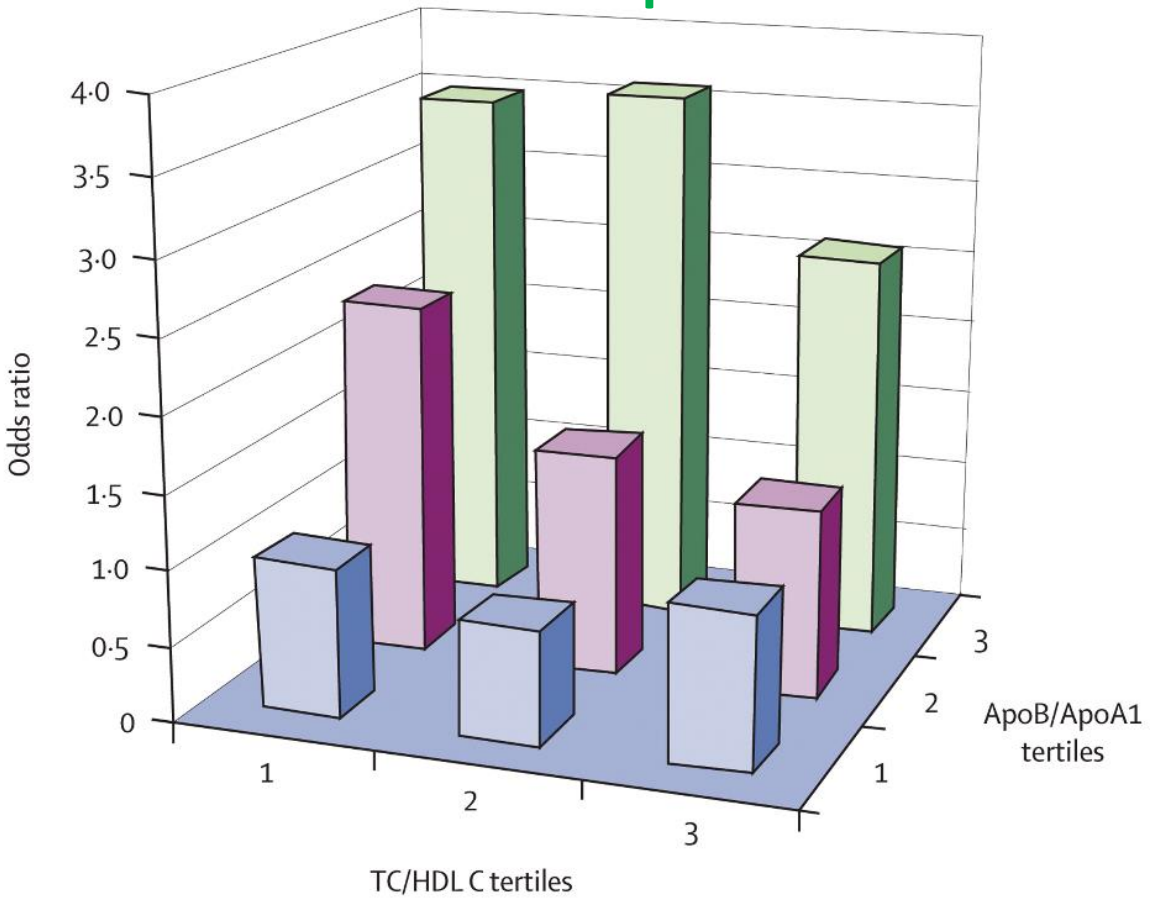
Phospholipids Cholesterol Triglyceride

Dyslipidemia and atherogenesis

Blood ↓ **lipoprotein levels** are considered **cardioprotective factors**:

HDL-cholesterol (**HDL-C**)

apoprotein A1 (**apo A1**)



	TC/HDL C tertile 1	TC/HDL C tertile 2	TC/HDL C tertile 3
ApoB/ApoA1 tertile 1	1·00	0·75 (0·65–0·88)	1·02 (0·75–1·38)
ApoB/ApoA1 tertile 2	2·36 (2·10–2·65)	1·49 (1·36–1·64)	1·26 (1·10–1·44)
ApoB/ApoA1 tertile 3	3·50 (2·47–4·96)	3·62 (3·25–4·03)	2·59 (2·37–2·82)

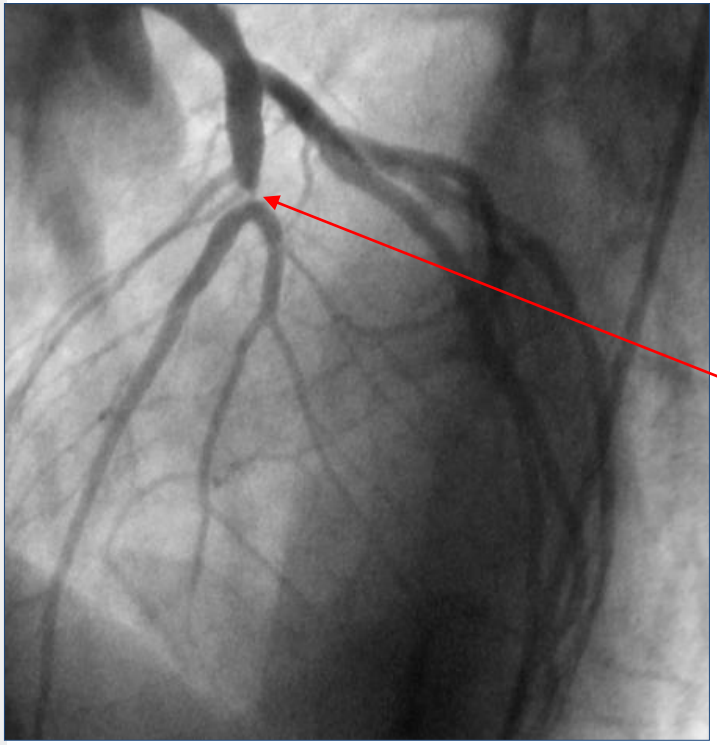
the INTERHEART case-control study

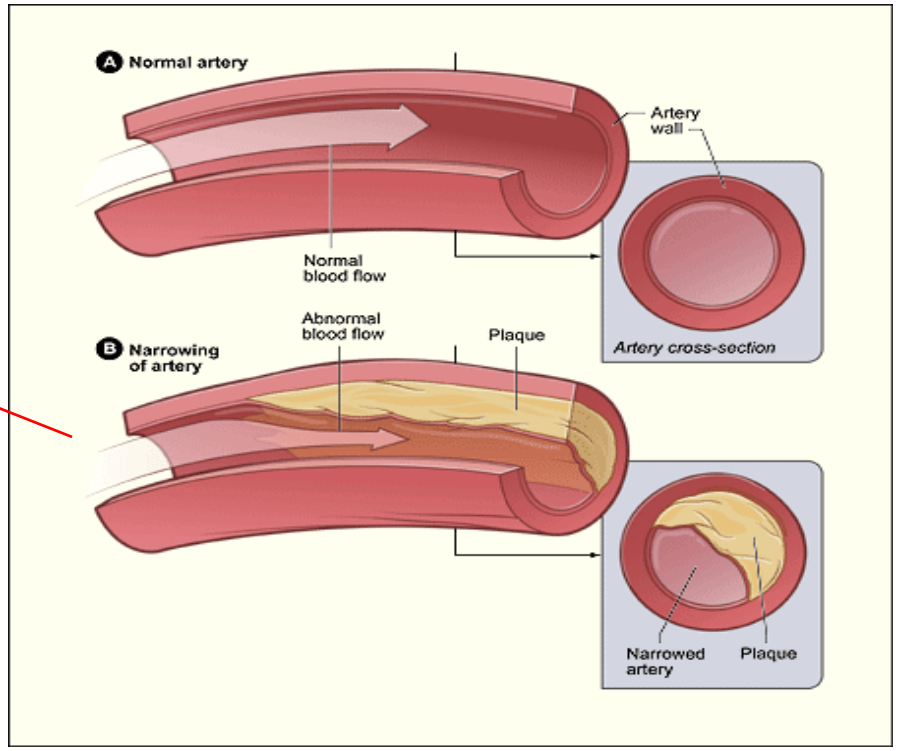
Atherosclerosis

From Greek **athêra**, porrridge and

σκλήρωσις, **sclerosis,** hardening

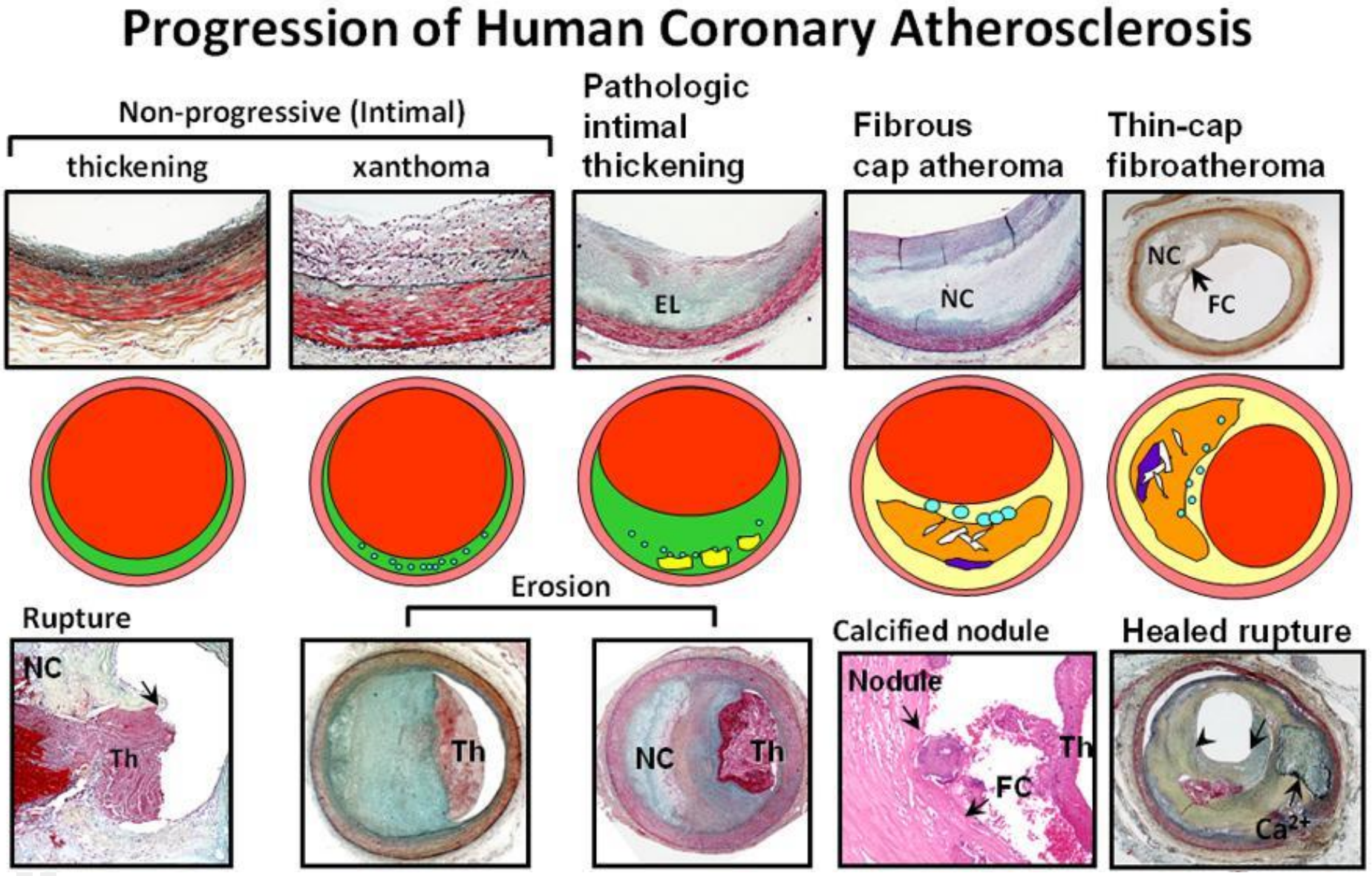
A build-up of plaque in the walls of the artery



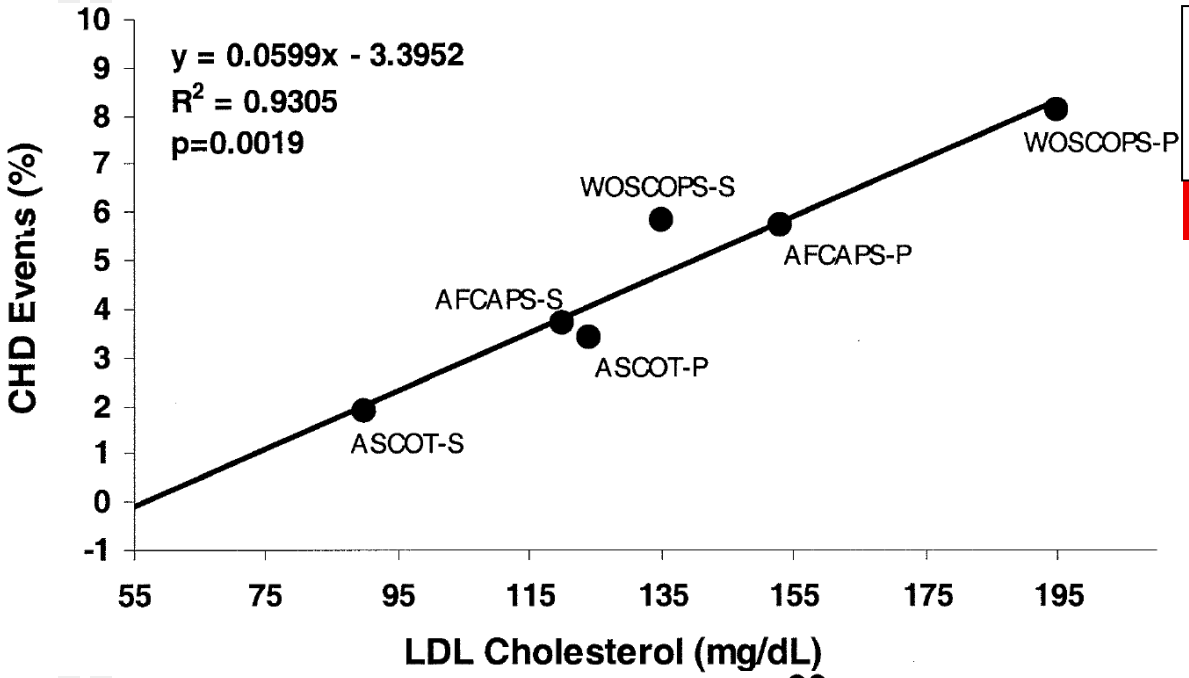


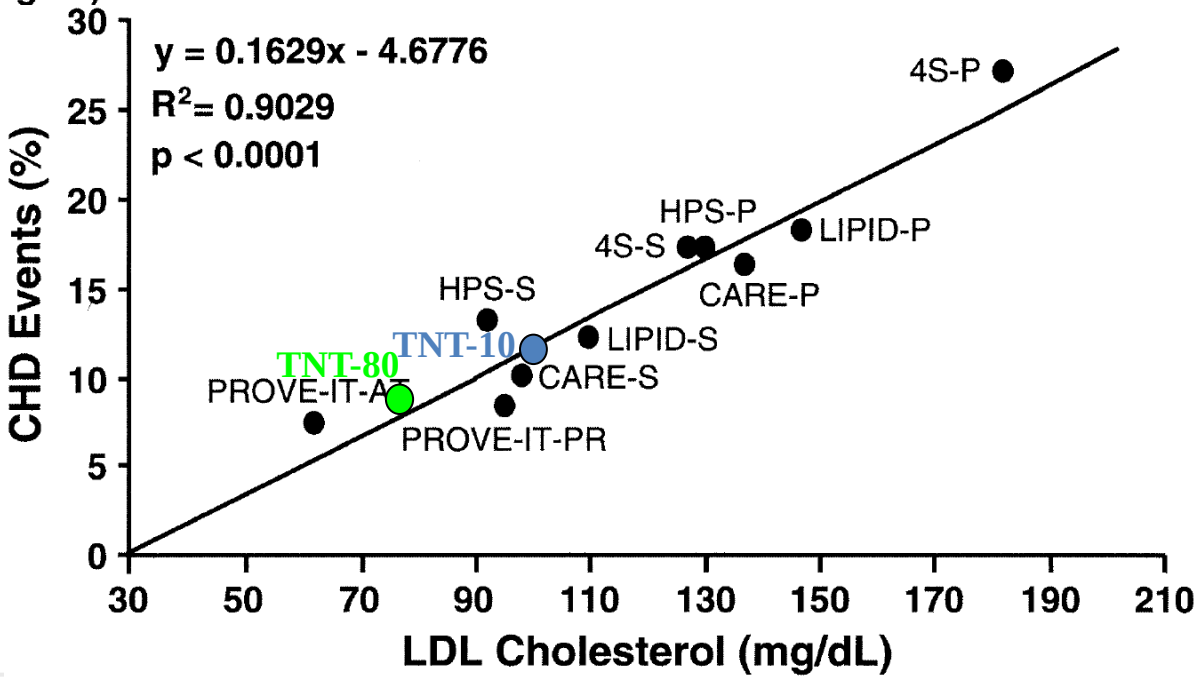
http://www.nhlbi.nih.gov/health/dci/Diseases/Atherosclerosis/Atherosclerosis_WhatIs.html

Histology


Progression of Human Coronary Atherosclerosis
Non-progressive (Intimal)
thickening
xanthoma
Pathologic intimal thickening
Fibrous cap atheroma
Thin-cap fibroatheroma
EL
NC
NC
FC
Rupture
Erosion
Calcified nodule
Healed rupture
NC
Th
Th
NC
Th
Nodule
Th
FC
Ca2+

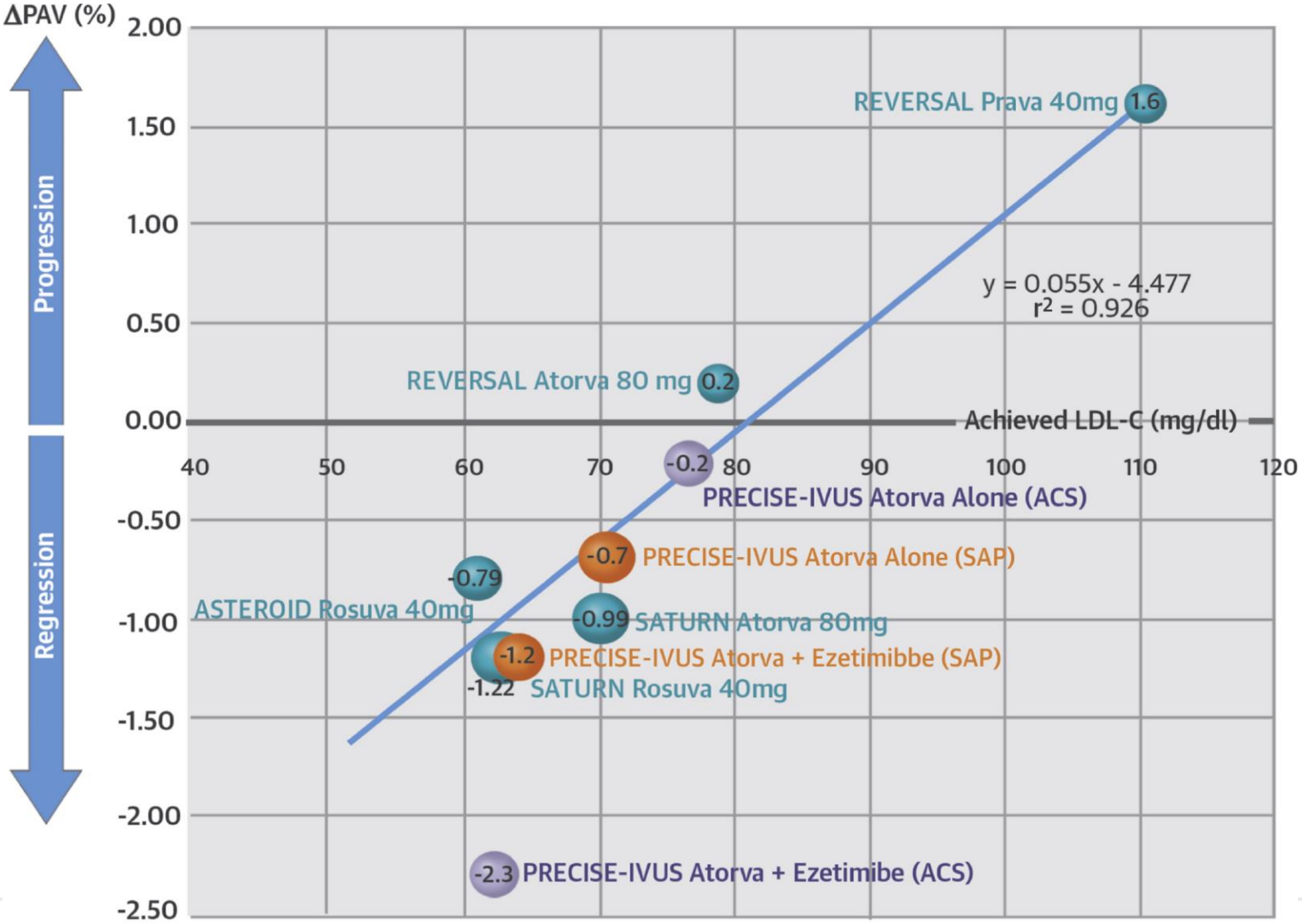
From primary prevention studies...





To secondary prevention studies...

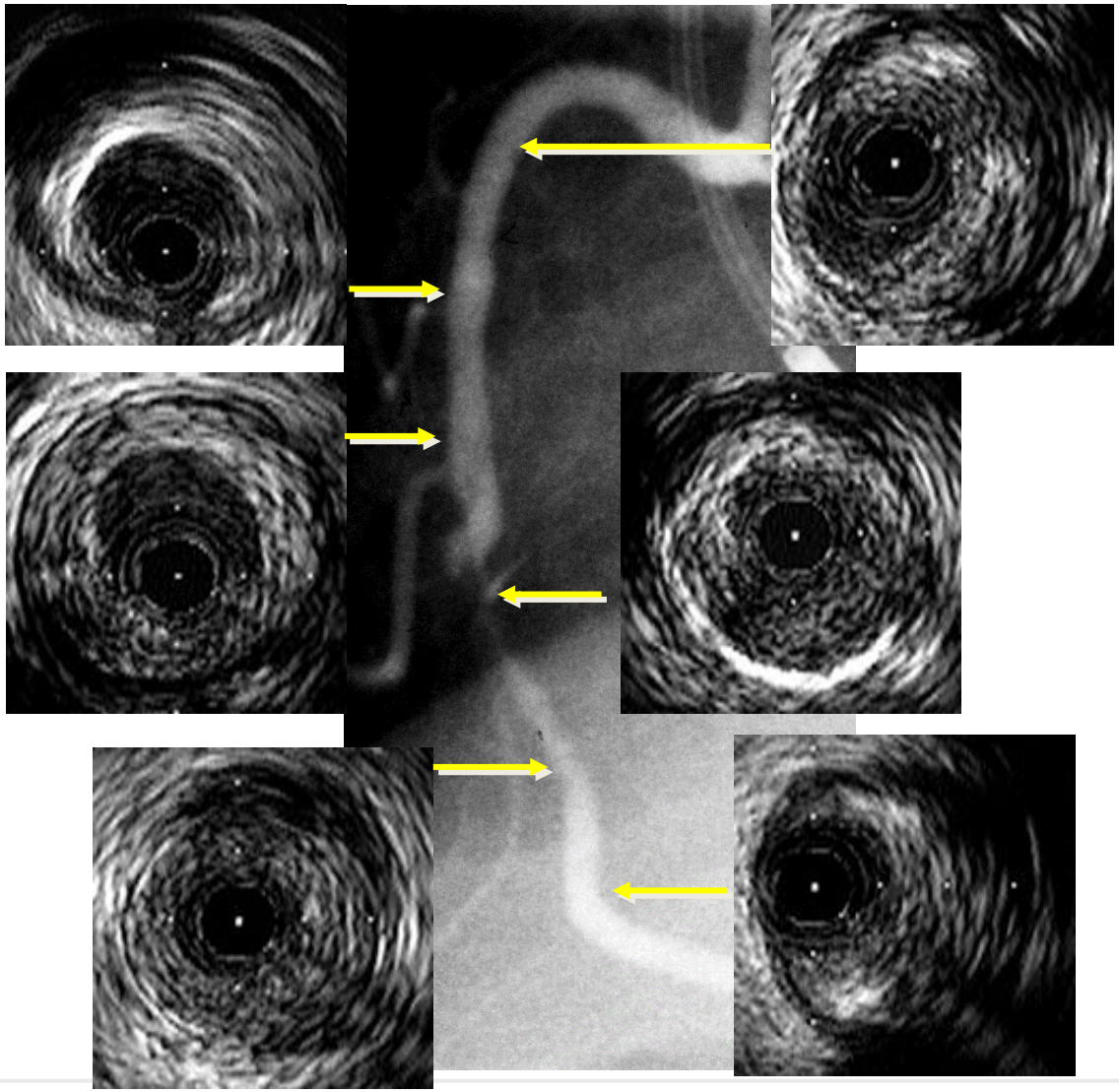
Plaque progression and regression by IntraVascular UltraSound (IVUS)



Tsujita K et al. J Am Coll Cardiol 2015; 66(5):495-507

In-vivo histology with IVUS

In apparently healthy arteries, there is 51±13% plaque



Mintz GS, et al. JACC 1995;25:1479-1485

Prevention of cardiovascular disease

First, target **high-risk populations**:

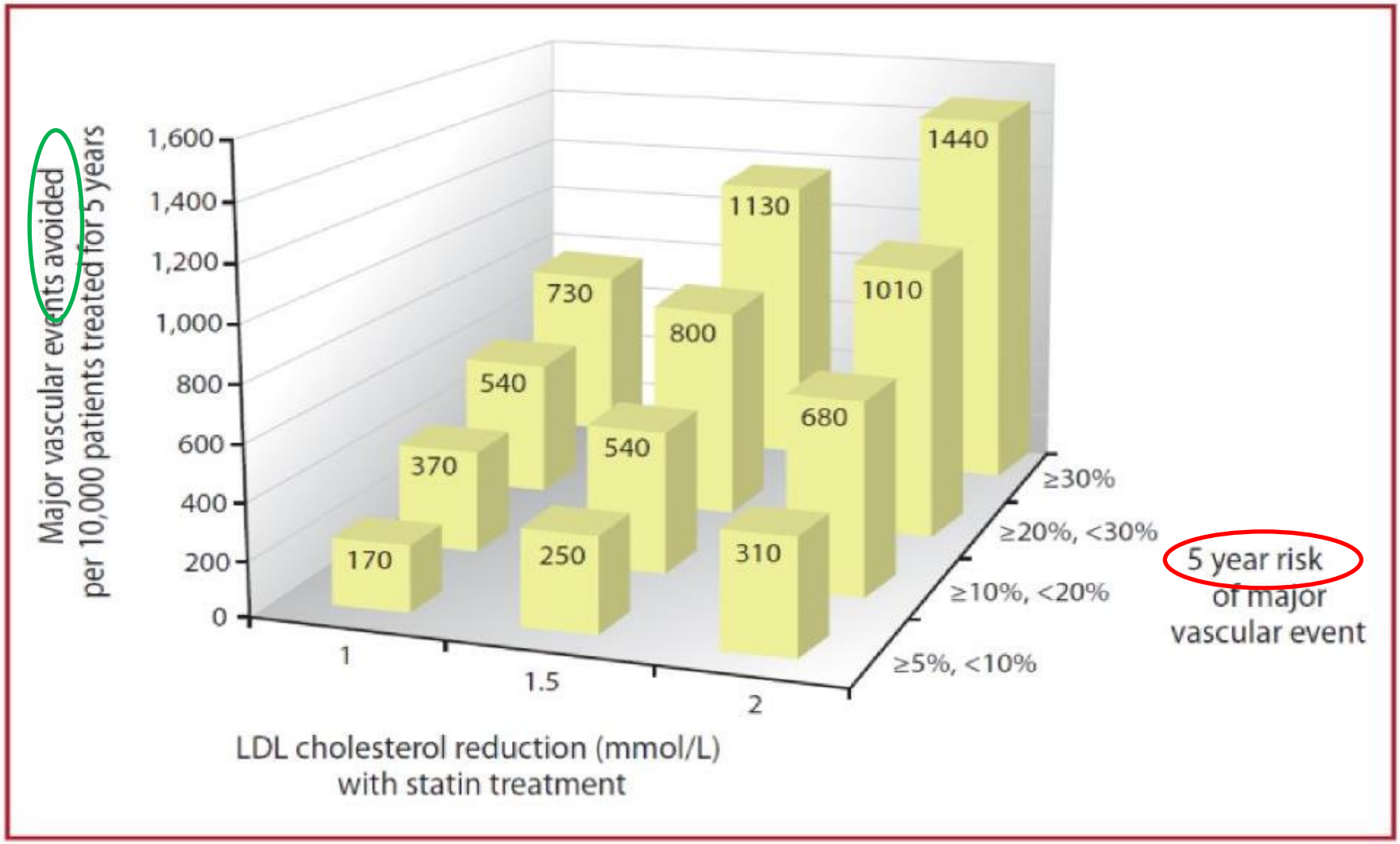
Primary:

- Familial hypercholesterolemia, early family history
- Diabetes and/or nephropathy
- Multiple Risk Factors

Secondary:

- Coronary
- Stroke
- Peripheral arterial disease

Cardiovascular disease complication rates can be reduced



Mach F, *et al. Eur Heart J*. 2019;0:1–78

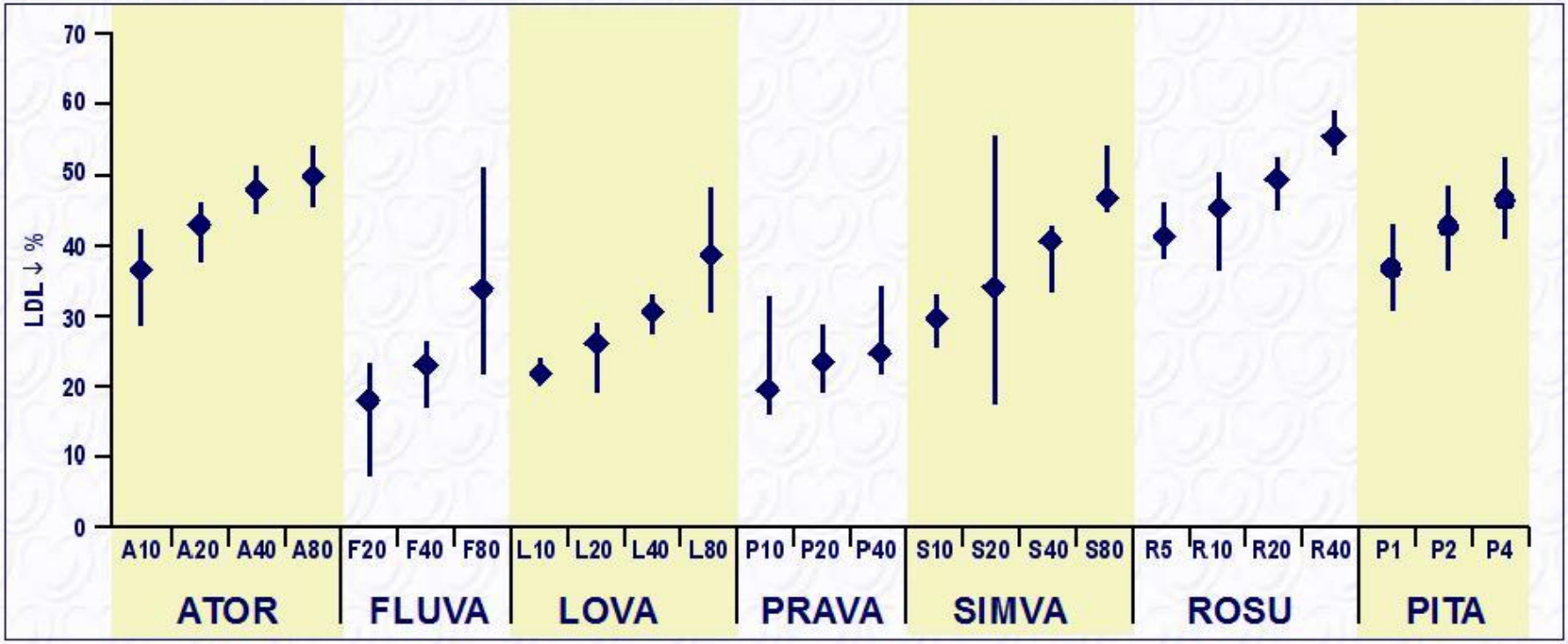
How to treat Hypercholesterolemia?

- Statins
- Ezetimibe
- Bempedoic Acid
- LDL-apheresis
- PCSK9-inhibitors

After excluding:

- Hypothyroidism
- Nephrotic syndrome
- Pregnancy
- Cushing syndrome
- Anorexia nervosa
- Immunosuppressant agents
- Corticosteroids

A systematic review and meta-analysis on the therapeutic equivalence of statins



Weng TC, et al. J Clin Pharm Ther. 2010;35;139-151
Mukhtar RY, et al. Int J Clin Pract. 2005;59(2):239-252

About a case: Mr C J né 17/3/1958

Antécédents familiaux

Père tombé mort dans les escaliers à 50 ans

Antécédents médicaux

At 56 years old

1/ Cardiopathie ischémique avec angor de novo 8/2014
20/8/2014 coronarographie:
- athéromatose diffuse modérée de l'IVA avec une lésion significative au niveau de l'IVAm -> 1 BMS (Prokinétic)
- athéromatose de la CX avec une lésion ostiale de 50% et une lésion de 50% au niveau de la 1ère marginale (petite branche)
- lésion 60% au niveau de l'IVP

Resténose proximalement au stent (détectée par CT coronaire). OCT: hyperplasie intimale dans BMS -> 1 long DES 3.0x38 mm

2/ Hypertension artérielle
3/ SAS

Traitement en cours

Tenormin mitis 50 1/j
Totalip 80mg 1/j
Asaflow 80mg 1/j
Forzaten 40/5 mg 1/j

Anamnèse

Bien, aucun angor

AP 1629 1512 Prélevé et encodé le **19/ 07/ 2016** à **16h 48**

Analyses		Résultats	Unités	Val. Références	Rés. 17.04.15	Antér 15.04.15
Chlore	+	110	mmol/l	96 - 105	107	107

Bilan lipidique
(normes selon le Belgian Lipid Club 2012)
NB: si risque cardiovasc.très élevé (mal.cardiov., diabète, ins.rénale): LDL<70 mg/dl.

Cholestérol		158	mg/dl	140 - 190	152
Cholestérol HDL		55	mg/dl	35 - 85	49
Cholestérol LDL (calculé)		80	mg/dl	60 - 115	76
Facteur de risque		2.9		0.0 - 4.0	3.1
Triglycérides		115	mg/dl	35 - 150	133

Conclusion

1) Cardiopathie ischémique stable. Seuil optimal de LDL <70 non atteint et probablement myalgies sur haute dose de statine -> switch vers Atozet 20/10 à l'essai 1 mois
Ergométrie après sevrage BB prévue le 15/2; Contrôle labo une semaine avant

2) HTA très bien contrôlée
EMU/protéinurie aussi prévu

Dernière consultation: Mr C J né 17/3/1958

Hb glycosylée A1c	**5,6**	%	4,0 - 6,0

Valeurs de référence:

Valeurs normales:	< 42 mmol/mol (< 6.0%)
Zone grise (non diabétique):	42 - 48 mmol/mol (6.0 à 6.5%)
Cible thérapeutique:	< 60 mmol/mol (< 7.6%)
Déséquilibre diabétique:	> 60 mmol/mol (> 7.6%)

Glycémie	**106**	H	mg/dL	70 - 105

LIPIDES

Triglycérides	**115**	mg/dL	< 150
Cholestérol total	**139**	mg/dL	< 190
Cholestérol HDL	**51**	mg/dL	> 40
Chol.total/Chol.HDL	**2,7**		< 4,9
Cholestérol "non HDL"	**88**	mg/dL	< 160
LDL Cholestérol (Friedewald)	**65**	mg/dL	< 115

On 20 mg atorvastatin and 10 mg ezetimibe – no more myalgia

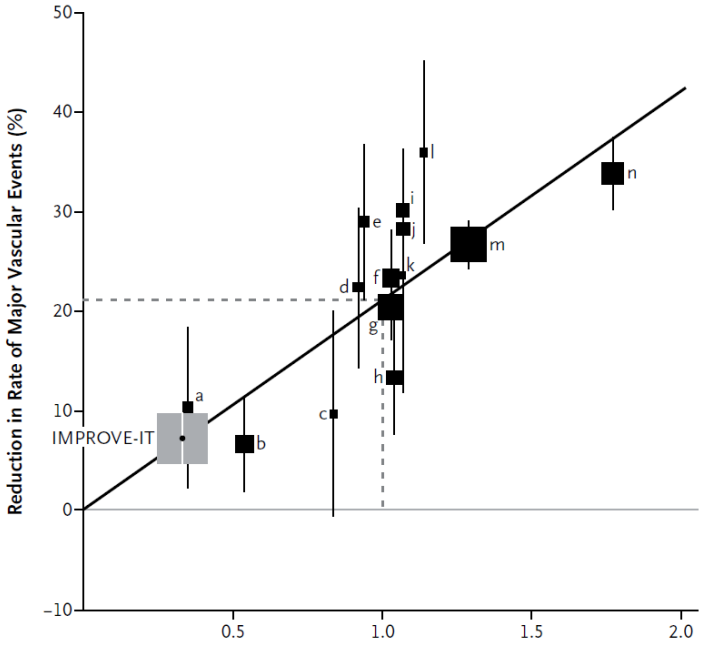
Etude IMPROVE-IT: simvastatine + ezetimibe

The NEW ENGLAND JOURNAL of MEDICINE

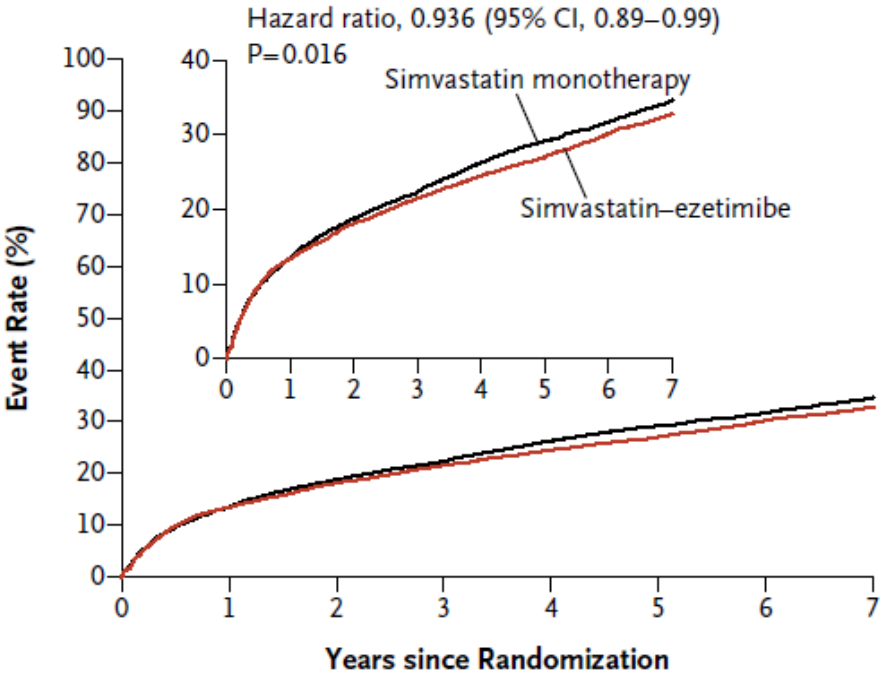
ESTABLISHED IN 1812 JUNE 18, 2015 VOL. 372 NO. 25

Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes

Christopher P. Cannon, M.D., Michael A. Blazing, M.D., Robert P. Giugliano, M.D., Amy McCagg, B.S.,



Disease (LIPID)[33]; h: Prospective Study of Pravastatin in the Elderly at Risk (PROSPER)[34]; i: Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA)[35]; j: West of Scotland Coronary Prevention Study (WOSCOPS)[36]; k: Post–Coronary Artery Bypass Graft (Post CABG)[37]; l: Collaborative Atorvastatin Diabetes Study (CARDS)[38]; m: Heart Protection Study (HPS)[2]; and n: Scandinavian Simvastatin Survival Study (4S)[1].



No. at Risk								
Simvastatin–ezetimibe	9067	7371	6801	6375	5839	4284	3301	1906
Simvastatin	9077	7455	6799	6327	5729	4206	3284	1857

Figure 1. Kaplan–Meier Curves for the Primary Efficacy End Point.

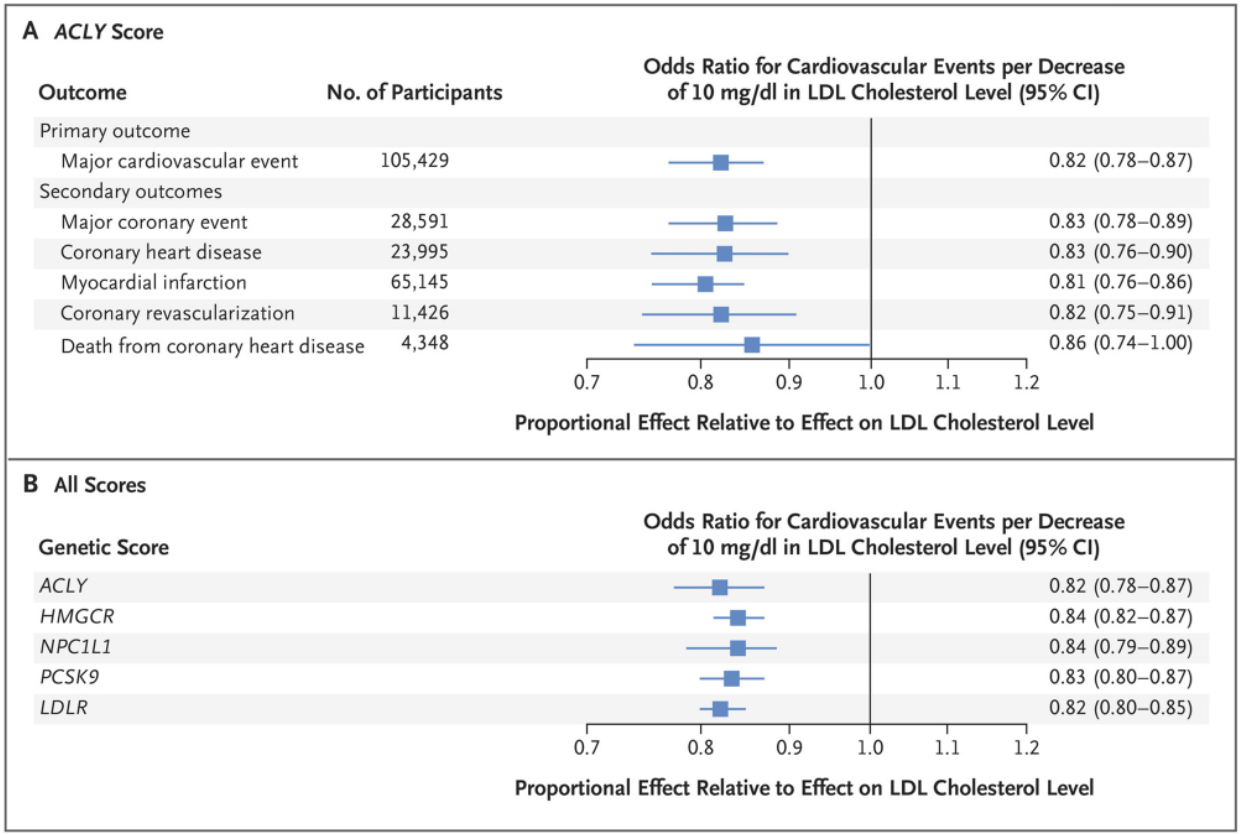
Shown are the cumulative event rates for the primary composite end point of death from cardiovascular disease, a major coronary event (nonfatal myocardial infarction, documented unstable angina requiring hospital admission, or coronary revascularization occurring at least 30 days after randomization), or nonfatal stroke in the intention-to-treat population during the overall study period (i.e., beginning from the time of randomization to

Bempedoic acid

- Blocks ATP citrate lyase upstream of *HMG-CoA reductase blocked by statins*

Mendelian Randomization Study of *ACLY* and Cardiovascular Disease

Brian A. Ference, M.D., Kausik K. Ray, M.D., Alberico L. Catapano, Ph.D., Thatcher B. Ference, Stephen Burgess, Ph.D., David R. Neff, D.O., Clare Oliver-Williams, Ph.D., Angela M. Wood, Ph.D., Adam S. Butterworth, Ph.D., Emanuele Di Angelantonio, M.D., John Danesh, D.Phil., John J.P. Kastelein, M.D., Ph.D., et al.



- Synergistic effect
- Or for Statin-intolerant

March 14, 2019
N Engl J Med 2019; 380:1033-1042

Familial hypercholesterolemia

Genetic disorders of lipoprotein metabolism

Disorder	Prevalence	Gene(s)	Effect on lipoproteins
HeFH[1]	I in 500	*LDLR* *PCSK9** *APO B*	↑ LDL
HoFH[2]	I in 10^6	*LDLR*	↑↑ LDL
FCH	I in 100/200	*USFI* + modifying genes	↑ LDL, ↑ VLDL ↑ APO B
Familial dysbetalipoproteinaemia	I in 5000	*APO E*	↑↑ IDL, chylomicron and VLDL remnants

1 Heterozygous familial hypercholesterolemia

2 Homozygous familial hypercholesterolemia

DLCN score

Family history

First-degree relative with known premature (<55 years, men; <60 years, women) coronary heart disease — Yes / No

First-degree relative with known LDL cholesterol >95th percentile by age and gender — Yes / No

Calculate 95th percentile

First-degree relative with tendon xanthoma and/or corneal arcus — Yes / No

Child(ren) <18 years with LDL cholesterol >95th percentile by age and gender — Yes / No

Clinical history

Subject has premature (<55 years, men; <60 years, women) coronary heart disease — Yes / No

Subject has premature (<55 years, men; <60 years, women) cerebral or peripheral vascular disease — Yes / No

Physical examination

Subject has tendon xanthoma — Yes / No

Subject has corneal arcus <45 years — Yes / No

DLCN score
6 (Probable FH)

LDL cholesterol

Use untreated LDL cholesterol: Calculate

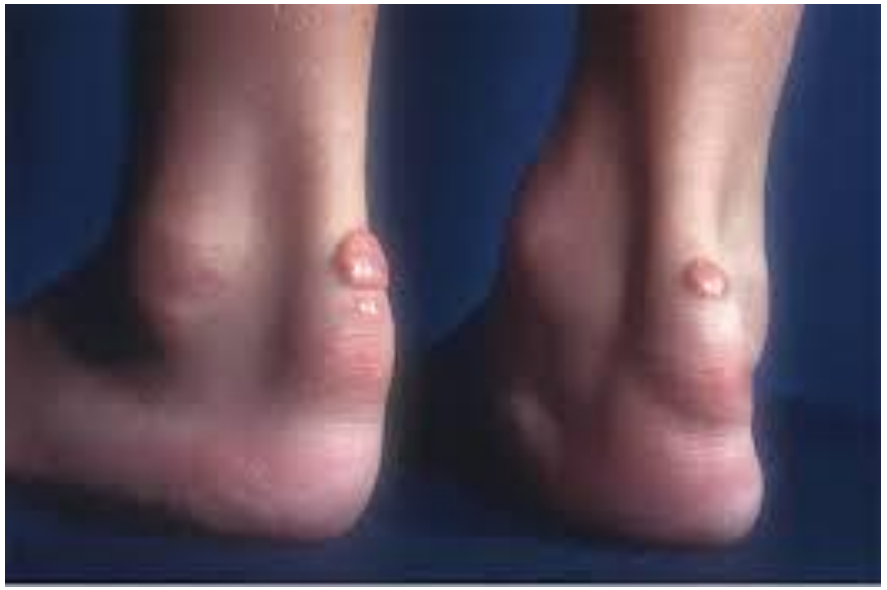
LDL cholesterol: 225 mg/dL

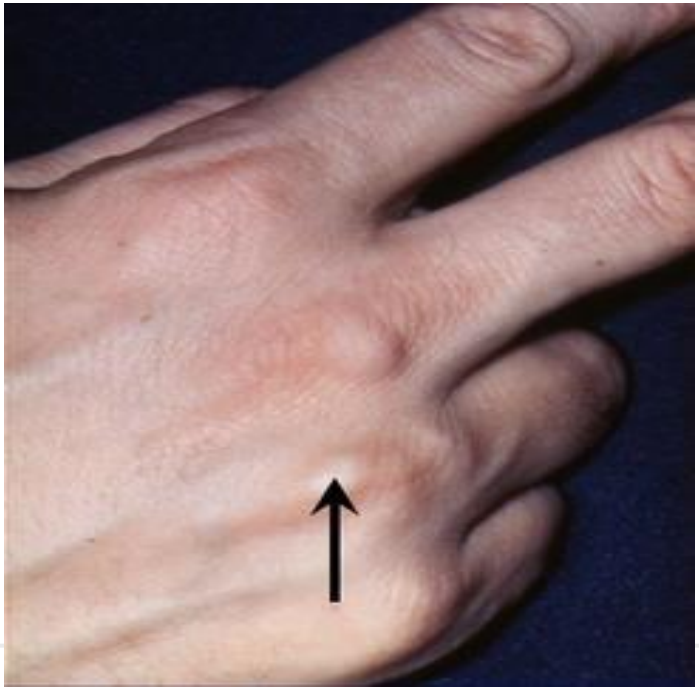
https:// www.lipidtools.com/calculator-pages/dlcn/

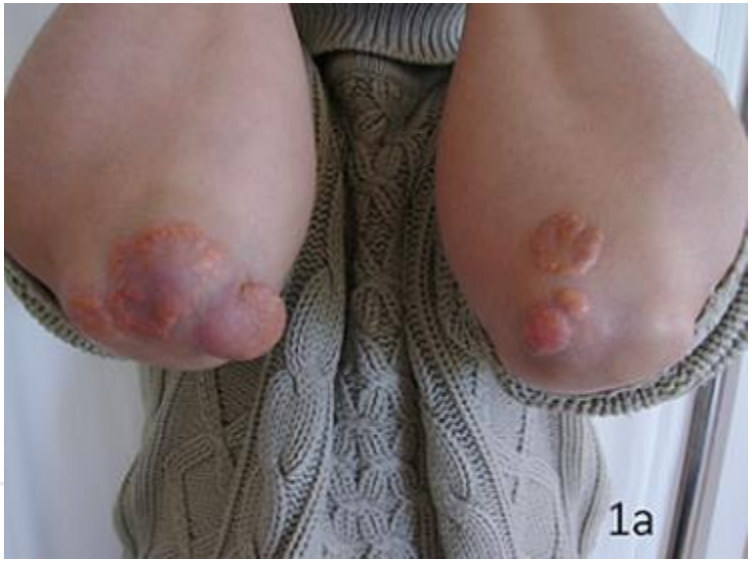
Clinical Examination

- ***Lipid deposits:***

Tendon Xanthomas







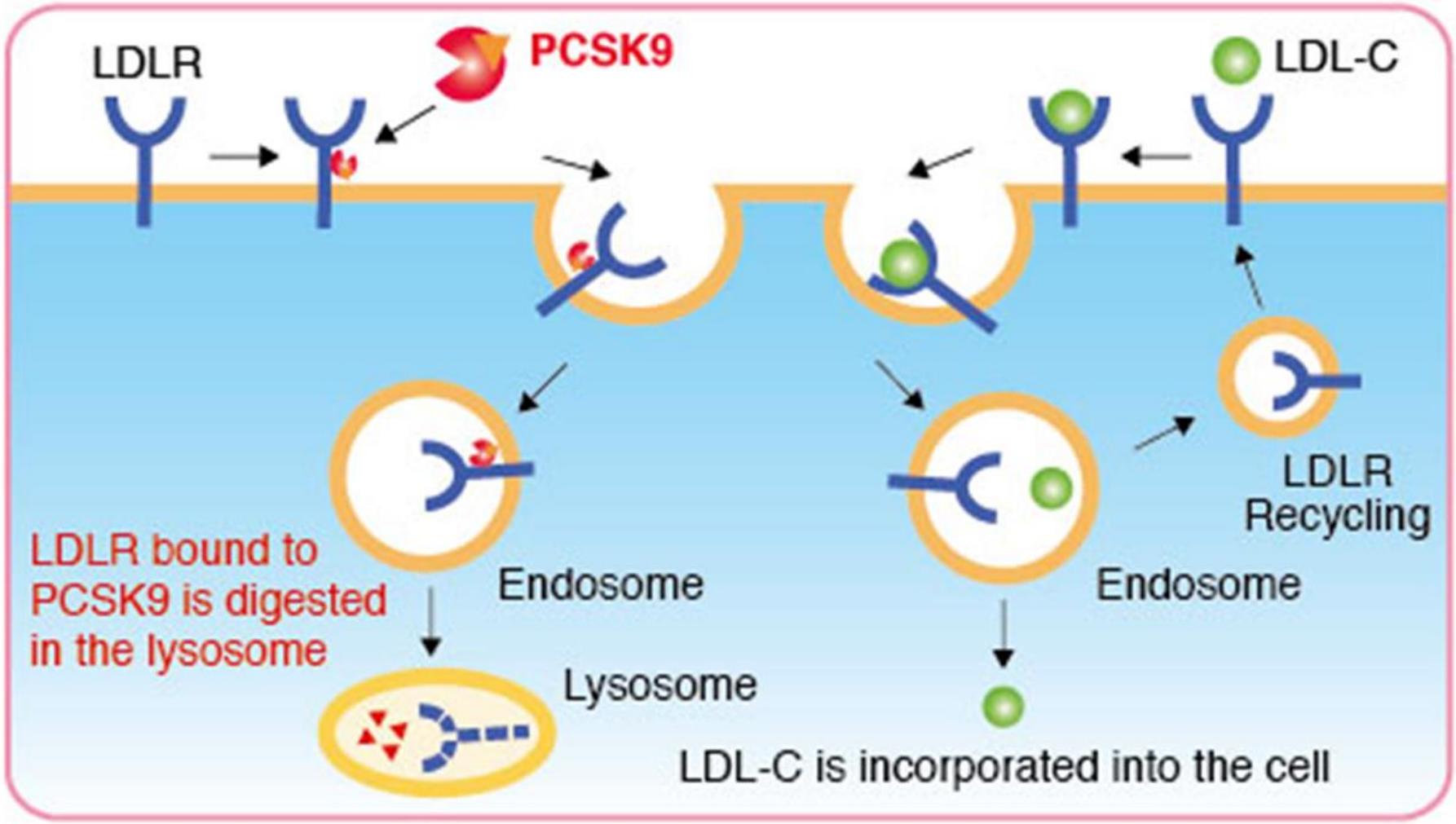
Untreated LDL estimation

LDL-cholesterol correction factor table for patients on statins ± ezetimbe medication.

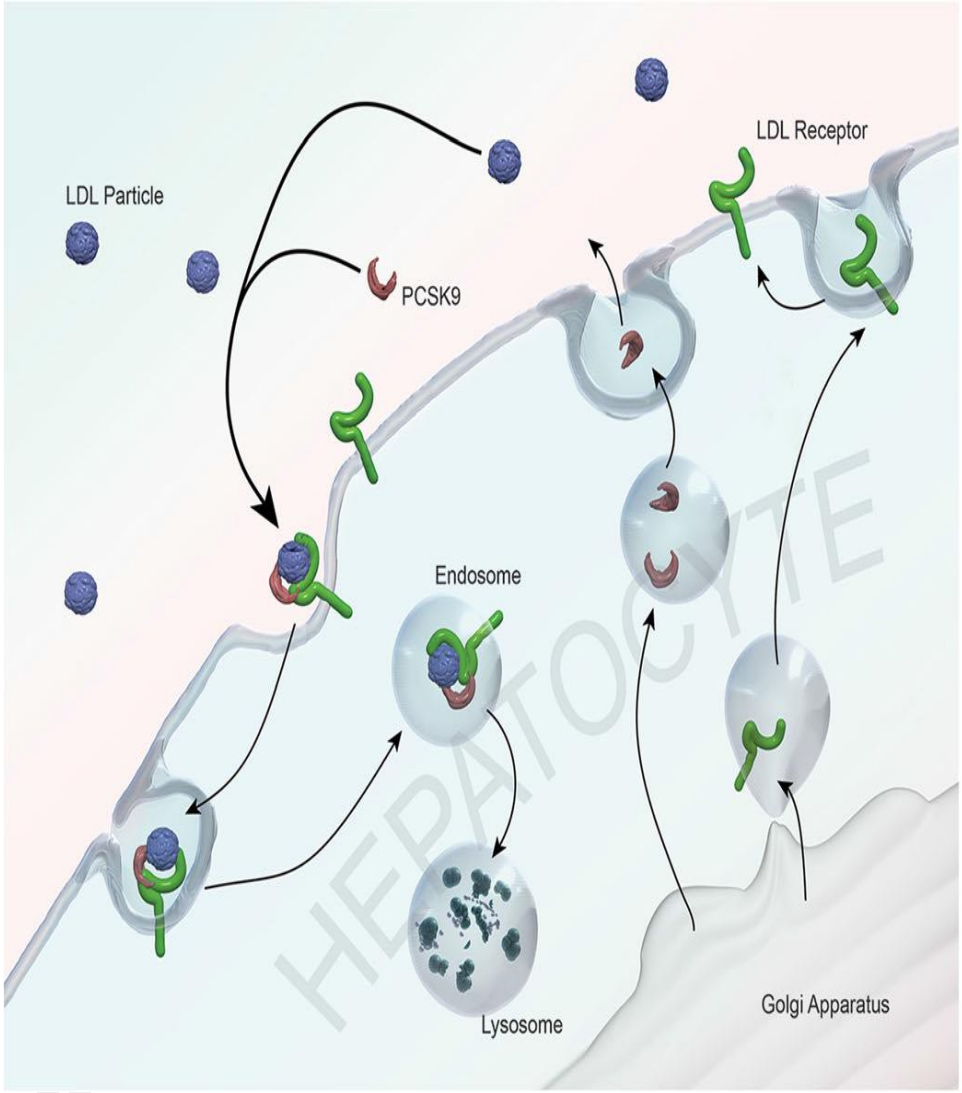
Statin/dose (mg)	Correction factor
Ezetimibe	
10	1.2
Pravastatin	
10	1.2
20	1.3
40	1.5
Pravastatin + Ezetimibe	
10 + 10	1.5
20 + 10	1.6
40 + 10	1.7
Simvastatin	
Simvastatin + Ezetemibe	
10 + 10	1.9
20 + 10	2.0
40 + 10	2.3
80 + 10	2.4
Rosuvastatin	
5	1.8
10	1.9
20	2.1
40	2.4
Rosuvastatin + Ezetimibe	
10 + 10	2.5
20 + 10	2.7
40 + 10	3.3

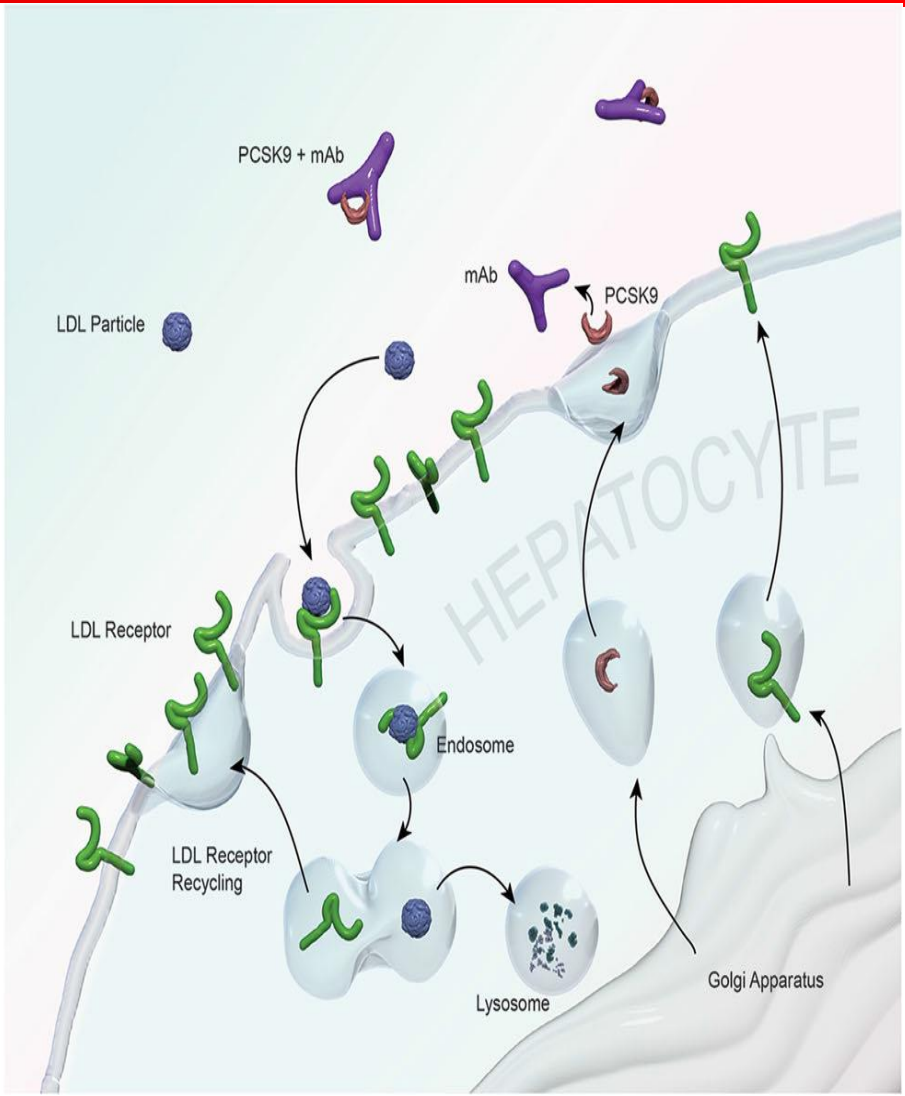
Clinical experience of scoring criteria for Familial Hypercholesterolaemia (FH) genetic testing in Wales K. Haralambos et al, Atherosclerosis Vol240, May 2015, Pages 190–196

PCSK9 inhibitors



PCSK9 inhibitors

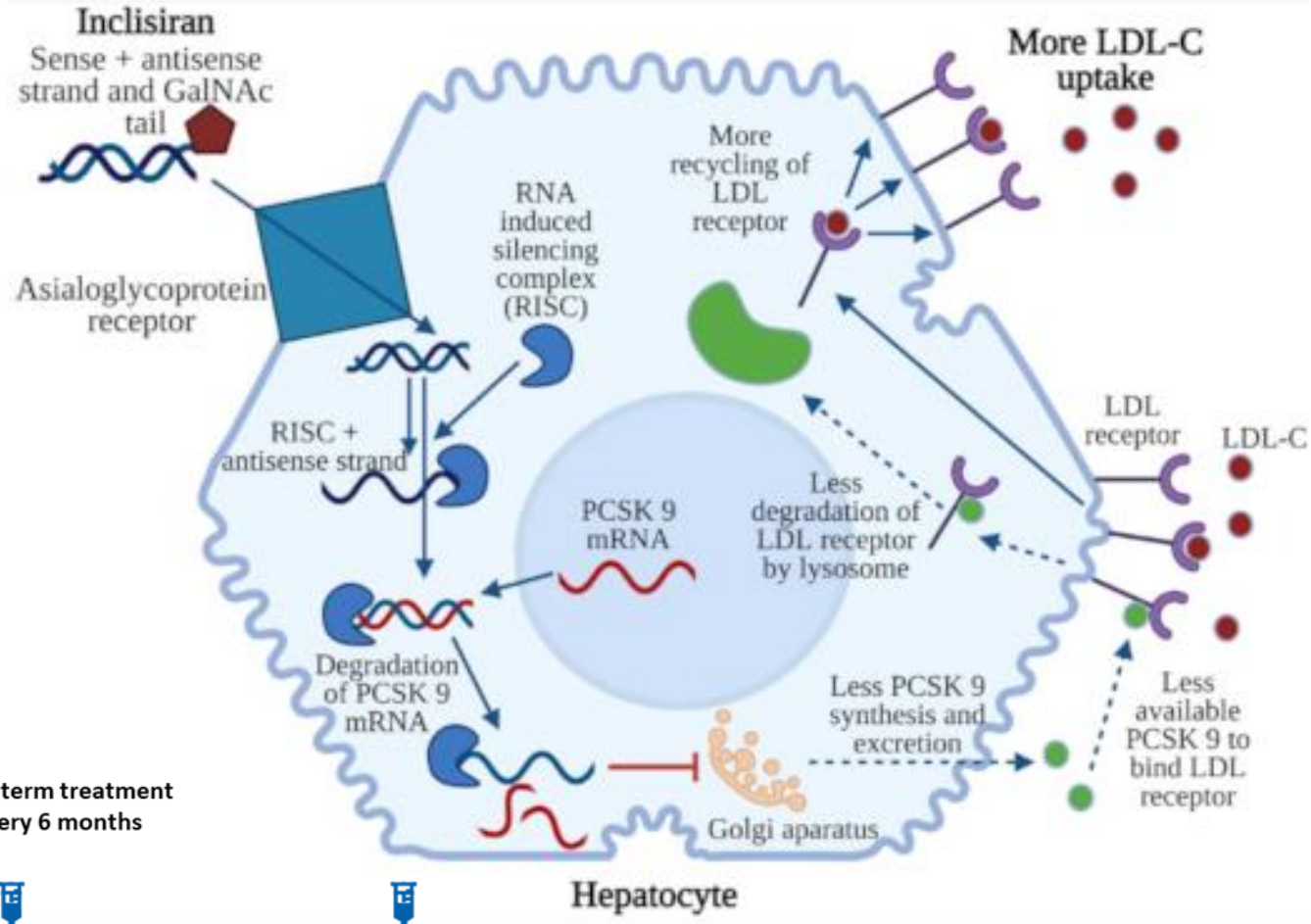




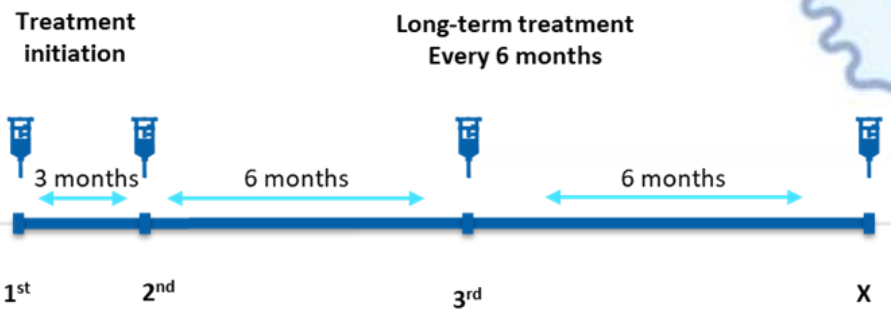
PCSK9 Inhibition: Current Concepts and Lessons from Human Genetics Fatima Rodriguez & Joshua W. Knowles

Novel inhibitor of PCSK9 synthesis

Inclisiran: small interfering RNA (siRNA)



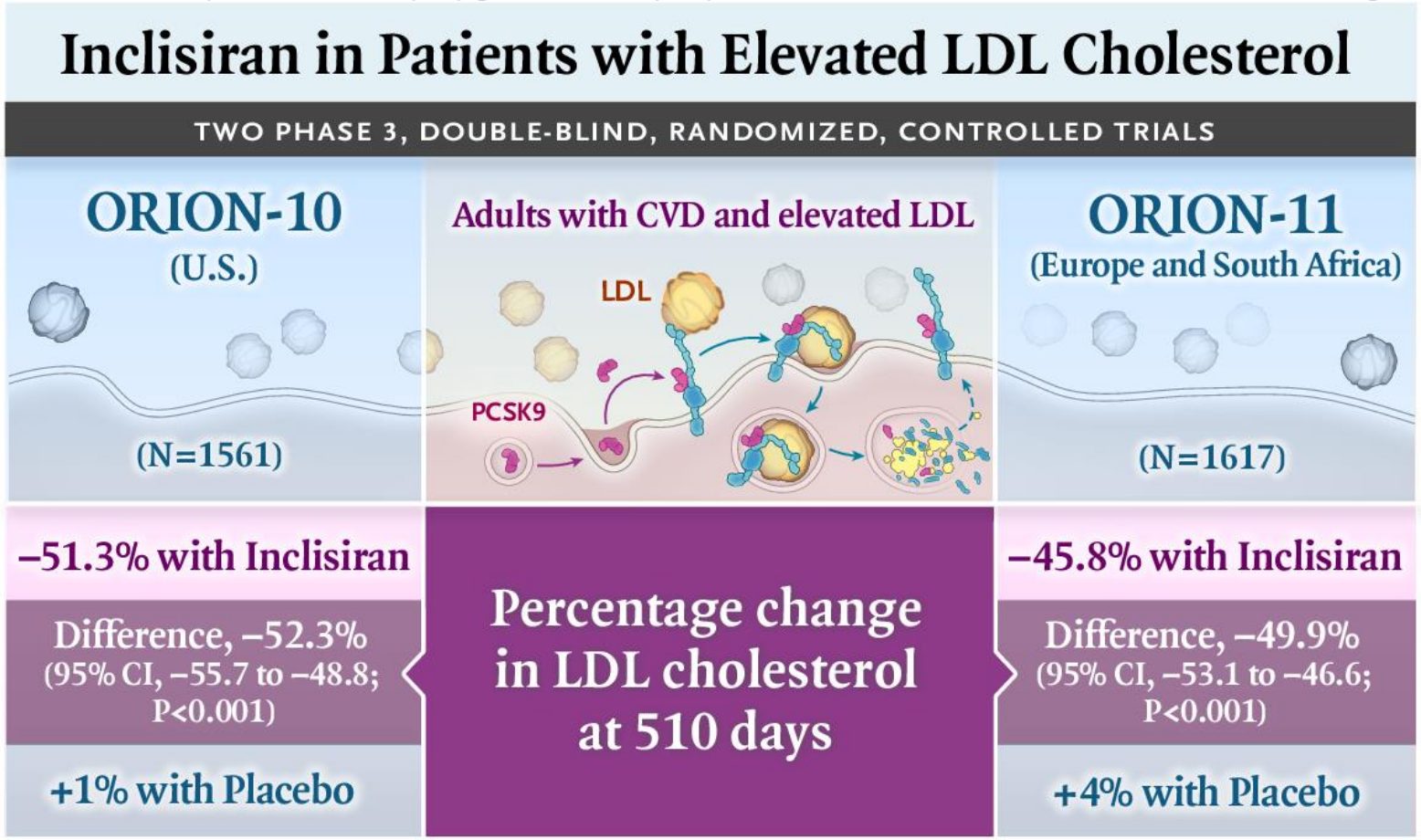
Dose regimen



Effects of Inclisiran on LDL

Two Phase 3 Trials of Inclisiran in Patients with Elevated LDL Cholesterol

Kausik K. Ray, M.D., M.Phil., R. Scott Wright, M.D., David Kallend, M.D., Wolfgang Koenig, M.D., Lawrence A. Leiter, M.D., Frederick J. Raal, Ph.D., Jenna A. Bisch, B.A., Tara Richardson, B.A., Mark Jaros, Ph.D., Peter L.J. Wijngaard, Ph.D., and John J.P. Kastelein, M.D., Ph.D. for the ORION-10 and ORION-11 Investigators*



Blocks Synthesis Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9)

April 16, 2020
N Engl J Med 2020; 382:1507-1519
DOI: 10.1056/NEJMoa1912387

About a case: Mr D V né 24/9/1967

Antécédents médicaux

Revascularisation par pontage (Ao-CD, Ao-diagonale, RIMA-OMCx, LIMA-IVA) le 15.11.2005. L'évolution post-opératoire a été caractérisée par un syndrome de vasodilatation excessif post-CEC, un épanchement pleural droit et un syndrome post péricardiotomie traité par corticothérapie, une embolie pulmonaire diagnostiquée fin décembre 2005. Dépression secondaire.

A 37 ans donc!

Récidive de douleurs atypiques avec ischémie démontrée. Coronarographie le 14.08.14: perméabilité des pontages (Ao-diagonale, LIMA-IVA) y compris le RIMA-OMCx. Néanmoins occlusion du pontage Ao-CD -> angioplastie de la CD native S2 et S3 et mise en place de 2 stents actifs DES.

9 ans post CABG…

Hypercholestérolémie familiale nécessitant une trithérapie. Hypercholestérolémie résiduelle.
Diabète II traité par régime.
Altération des tests de cytolyse sur stéatose (NASH).
Lésion du nerf fémorocutané D.
Douleurs pariétales résiduelles sur déhiscence sternale.
SAS modéré 12a/h, microéveils 24a/h ; bilan ORL en cours, envisager perte de

Traitement en cours

Emconcor 2.5mg par jour, Inegy 10/80mg par jour, Asaflow 80mg, Pantomed 20mg, Clopidogrel 75mg/j (98cp en cat B).
Suivi diététique.

Bilan lipidique

(normes selon le Belgian Lipid Club 2012)

NB: si risque cardiovasc.très élevé (mal.cardiov., diabète, ins.rénale): LDL<70 mg/dl.

Cholestérol	+	256	mg/dl	140 - 190
Cholestérol HDL	-	34	mg/dl	35 - 85
Cholestérol LDL (calculé)	+	185	mg/dl	60 - 115
Facteur de risque	+	7.5		0.0 - 4.0
Triglycérides	+	184	mg/dl	35 - 150

At 49 years old, with CABG < 12 years old
on 80 mg Simvastatin
and 10 mg Ezetemibe

Untreated LDL Assessment

LDL-cholesterol correction factor table for patients on statins ± ezetimbe medication.

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20 + 10	2.7
40 + 10	3.3

Clinical experience of scoring criteria for Familial Hypercholesterolaemia (FH) genetic testing in Wales K. Haralambos et al, Atherosclerosis Vol240, May 2015, Pages 190–196

Taux de LDL-C	
>325 mg/dl	8
251–325 mg/dl	5
191–250 mg/dl	3
155–190 mg/dl	1
Analyse génétique moléculaire (analyse ADN)	
Mutation causale observée dans le gène du LDLR, de l'APOB ou du PCSK9	8

At 49 years old, with CABG < 12 years old **2 points**
on 80 mg Simvastatin
and 10 mg Ezetrol
with LDL estimated at 185 x 2.4= 444 **8 points**

Total: 10 points


GIVE ME MORE!
memegen.com