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DUBAI | UAE | 22 to 24 APRIL

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Unlocking Cardiovascular Health: Spotlight on Lipid Management in Primary Care

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ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol.

CASES

37 F

Asymptomatic

Father and parental uncle had premature CAD (3 vd at age 49)

TC 209, TG 59, HDL 64, LDL 133

After life style changes

TC 184, TG 82, HDL 50, LDL 118

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DM 5 years, HTN, No IHD, DLP

Asymptomatic

TC 242, TG 288, HDL 45, LDL 139

Meds : Pitavastatin 2, ezetimibe 10, gliclazide 120, saxagliptin 5, telmisartan 160, amlodipine 5

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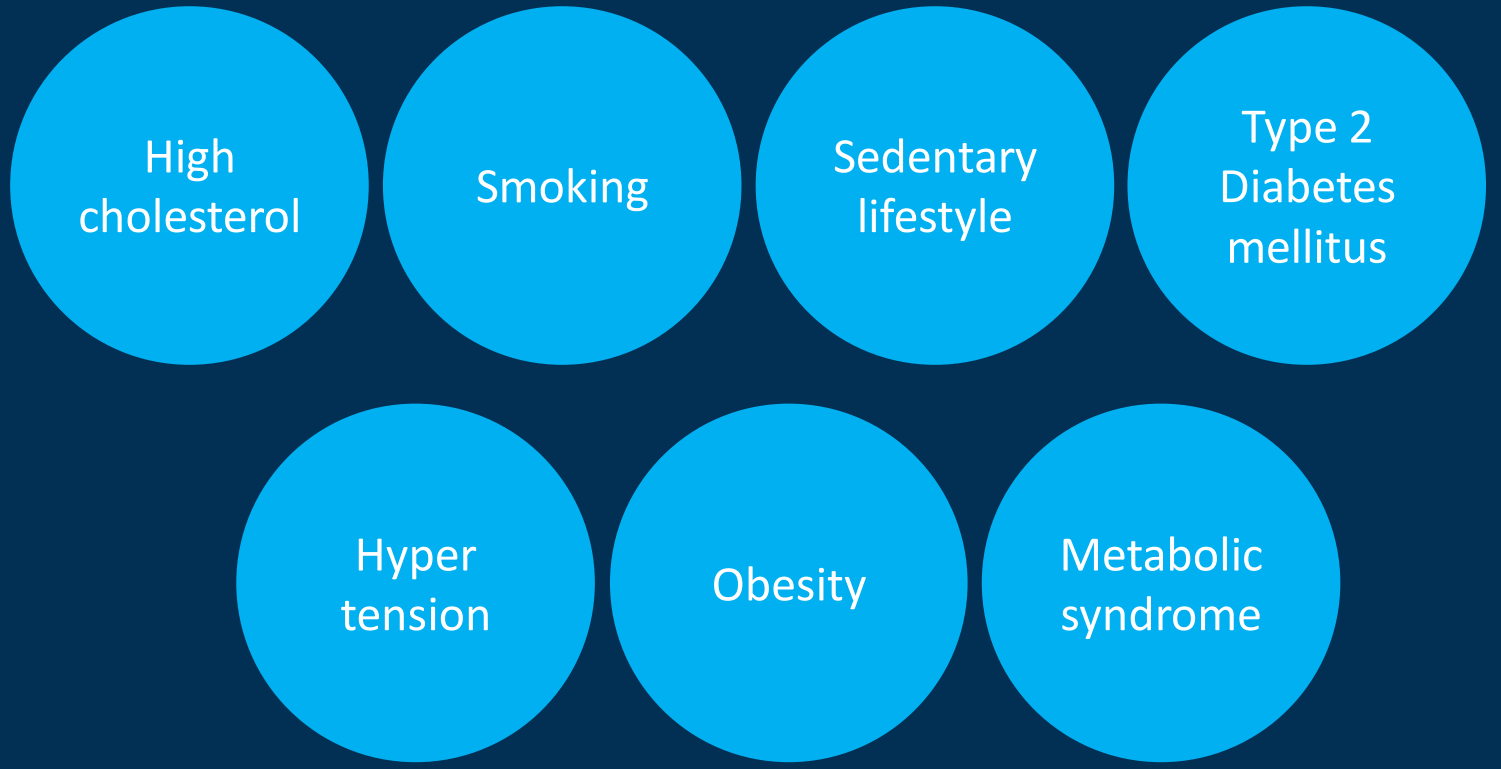
58 m

DM, HTN, CKD (eGFR 26), TVD post CABG sept 2023, PVD

TC 206, TG 520, HDL 32, LDL 100

Meds: atorvastatin 80, ezetimibe 10, clopidogrel 75, rivaroxaban 15, bisoprolol 2.5, amlodipine 5, insulin

Middle East faces a heavy burden of CV risk factors



DYSIS I[1]

DYSIS II[2]

References: 1. Al Sifri SN, et al. PLoS One. 2014;9(1):e84350. **2.** Al Mahmeed W, et al. Heart Views. 2019;20(2):37-46.

UNITED ARAB EMIRATES [1]

2016 TOTAL POPULATION: 9 270 000
2016 TOTAL DEATHS: 15 000

As per 2019 statistics;[2]

A **mortality rate due to cardiovascular diseases** reaching **147.9** per 100,000 inhabitants, up to **3 times higher than UK or Australia**

A **diabetes prevalence ratio** reaching **17.3%** (in population aged 20 to 79),

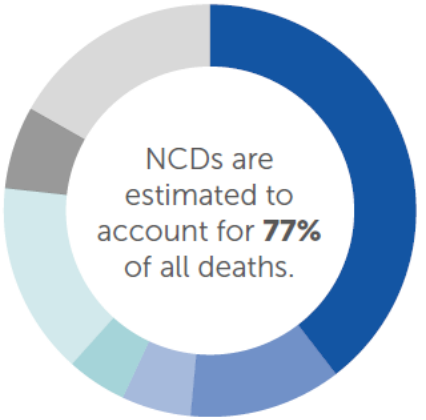
i.e. **2 to 4 times higher than Australia or the UK**

A **prevalence of overweight** in adults of **34.5%**, equivalent to **5 to 10 times the same ratio in Singapore or Japan**

A prevalence of **cigarette smoking adults** of **21.9%**, at least **3.8 pts more than in some developed countries**

PROPORTIONAL MORTALITY*

- 40% Cardiovascular diseases
- 15% Other NCDs
- 12% Cancers
- 6% Communicable, maternal, perinatal and nutritional conditions
- 5% Chronic respiratory diseases
- 17% Injuries
- 5% Diabetes



14 500 LIVES CAN BE SAVED BY 2025 BY IMPLEMENTING ALL OF THE WHO "BEST BUYS"

1. World Health Organization - Noncommunicable Diseases (NCD) Country Profiles, 2018 https://www.who.int/nmh/countries/are_en.pdf?ua=1
2. Dubai health Investment guide2019 https://www.dha.gov.ae/Asset%20Library/27012019/eng.pdf

CVD is largely preventable

Modifiable CV risk factors account for 90% of risk myocardial infarction[1]

Modifiable CVD risk factors are well defined

BP, lipids, diabetes, smoking, abdominal obesity, psychosocial factors, physical inactivity, diet, etc[1,2]

Absolute CVD risk management most effective

Potentially twice as many deaths from coronary heart disease prevented compared to single risk factor approach[3]

Targeting therapy to highest risk groups creates greatest benefit

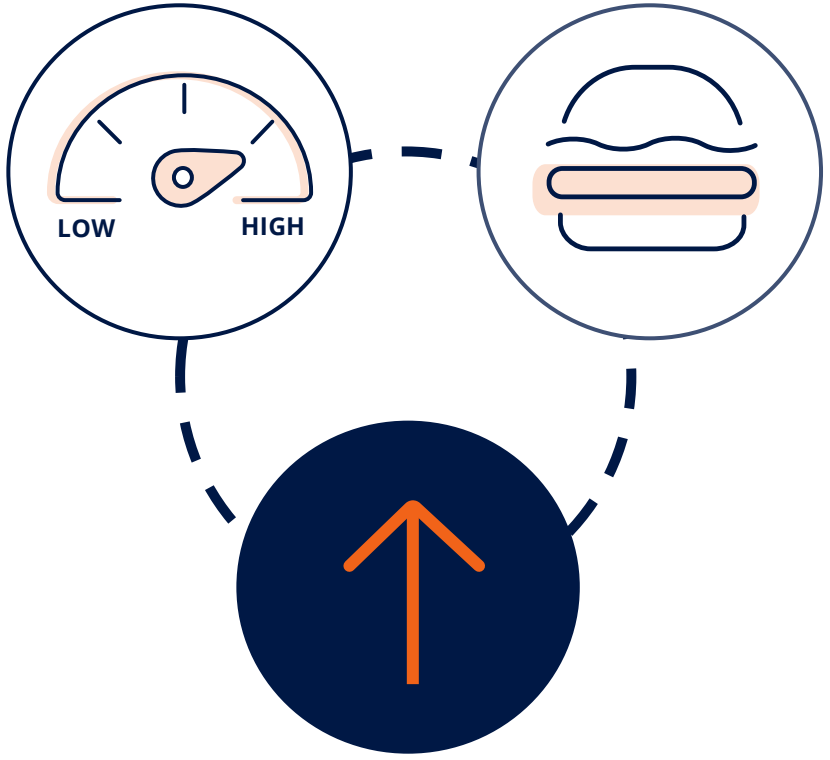
Absolute risk reduction is greatest when BP and cholesterol treatment is targeted to patients with highest baseline risk[2]

CVD risk calculators are essential

Risk calculators are useful in guiding treatment and are more accurate than clinical judgement[4]

LDL-C is one of the top modifiable risk factors* for CVD[1,2]

High systolic blood pressure



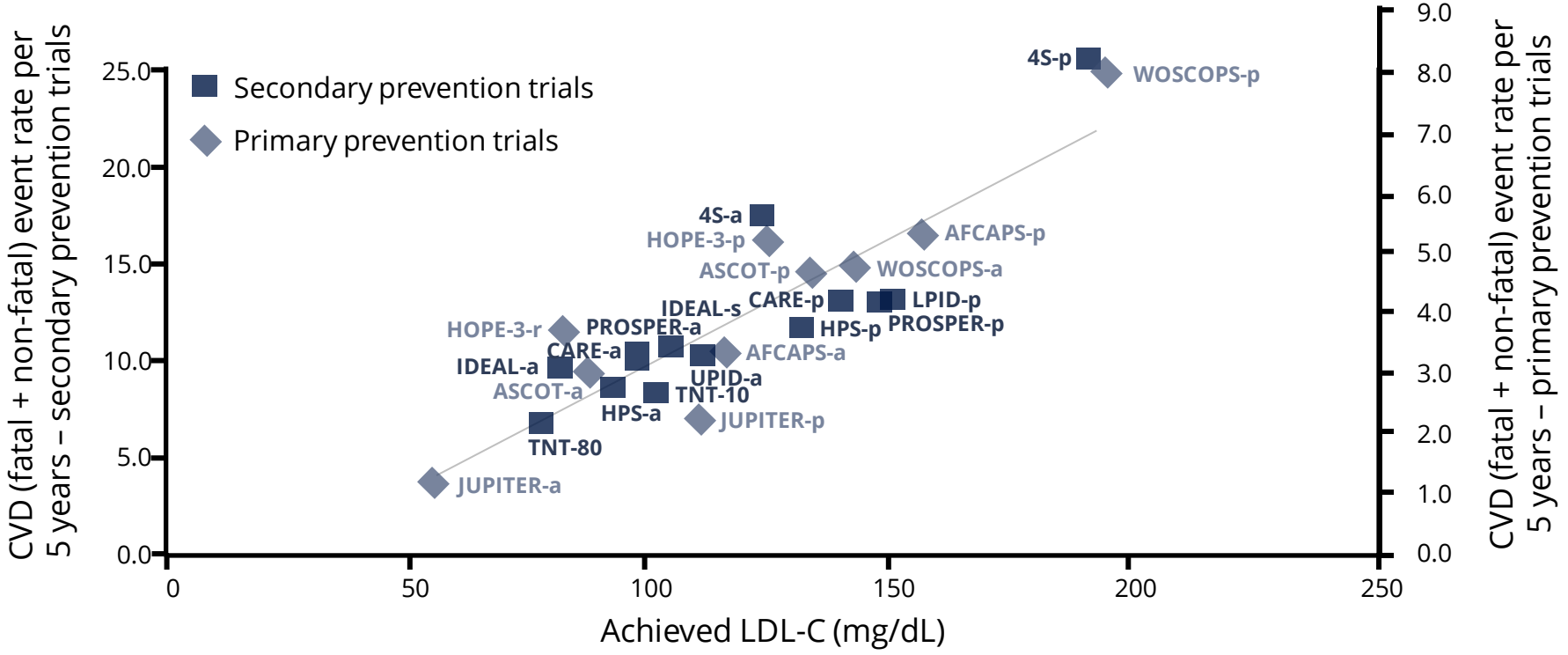
Diet

High LDL-C

Other risk factors include:
- Air pollution
- Smoking
- High body-mass index

*2019 ranking for CVD burden attributable to modifiable risk factors: High systolic blood pressure, dietary risks, high LDL-C, air pollution, tobacco, high body-mass index, high fasting plasma glucose, kidney dysfunction, non-optimal temperature, other environmental risks, alcohol use, low physical activity.[1]
CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol.
1. Roth GA et al. *J Am Coll Cardiol*. 2020;76:2982–3021; 2. Ference BA et al. *J Am Coll Cardiol*. 2018;72:1141–56.

Multiple clinical trials have confirmed a correlation between LDL-C and the rate of CV events



CV, cardiovascular; CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol. .
Ference BA et al. *Eur Heart J*. 2017;38:2459–72.

Target achievement is worse for secondary prevention compared to primary prevention

SECONDARY[1]

67%

of patients on secondary prevention in the GULF region do **not** achieve their lipid targets*

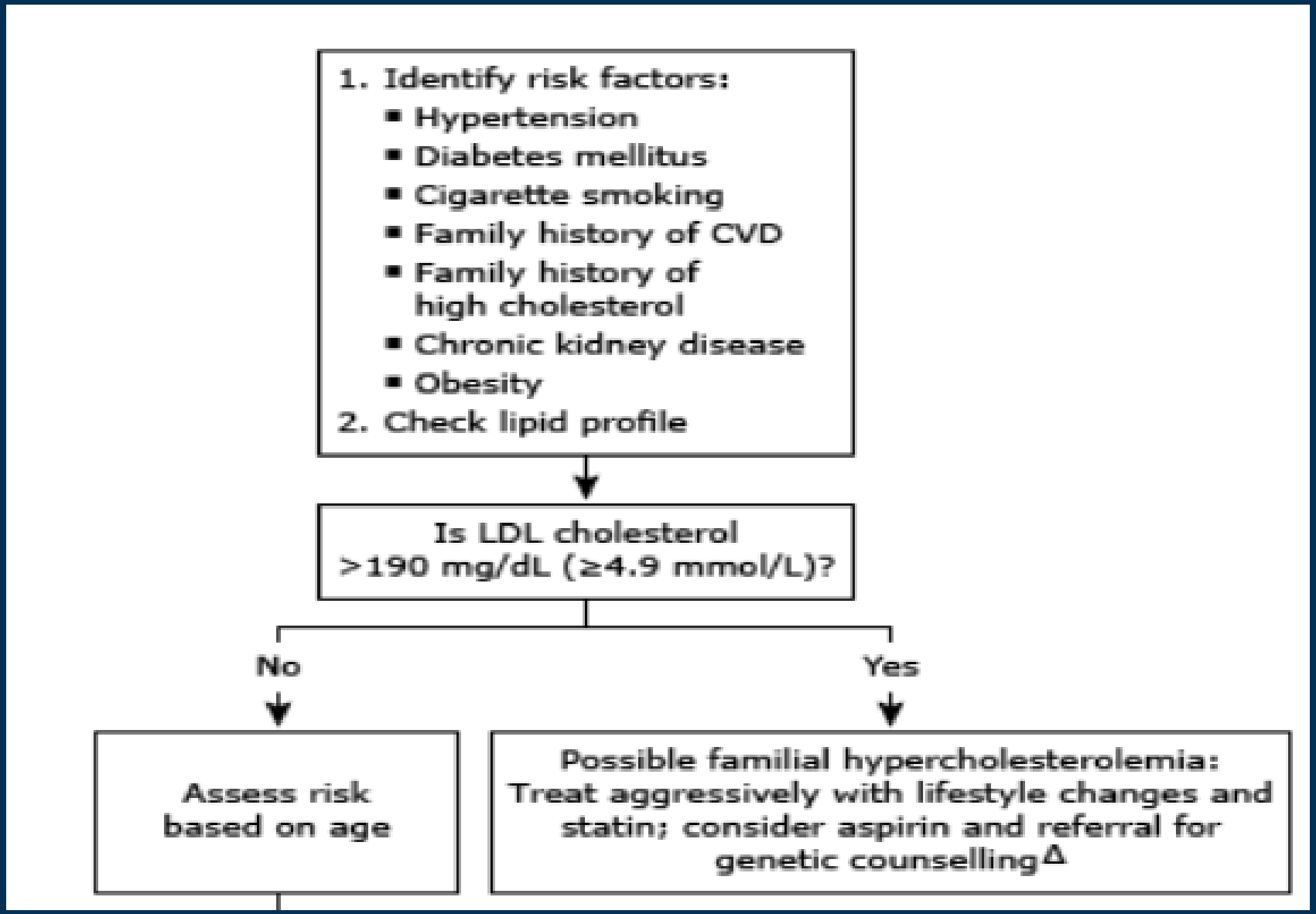
PRIMARY[1]

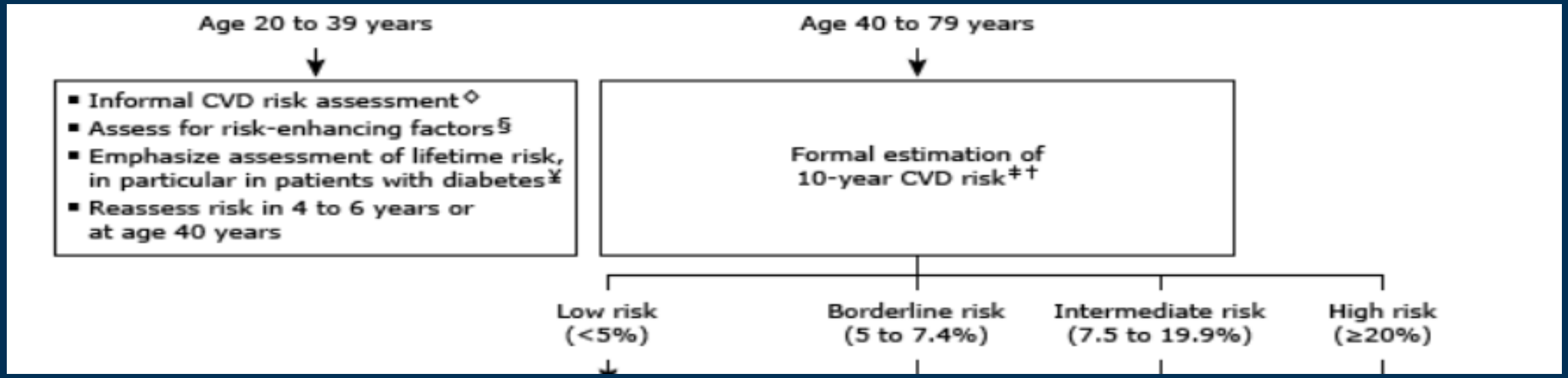
41%

of patients on primary prevention in the GULF region do **not** achieve their lipid targets*

*2004 updated NCEP-ATP-III guidelines

References: 1. Arafah M, et al. Angiology. 2014;65(10):919-926.


1. Identify risk factors:
Hypertension
Diabetes mellitus
Cigarette smoking
Family history of CVD
Family history of high cholesterol
Chronic kidney disease
Obesity
2. Check lipid profile
Is LDL cholesterol >190 mg/dL (≥4.9 mmol/L)?
No
Yes
Assess risk based on age
Possible familial hypercholesterolemia: Treat aggressively with lifestyle changes and statin; consider aspirin and referral for genetic counselling Δ


Age 20 to 39 years
Age 40 to 79 years
Informal CVD risk assessment◇
Assess for risk-enhancing factors§
Emphasize assessment of lifetime risk, in particular in patients with diabetes¥
Reassess risk in 4 to 6 years or at age 40 years
Formal estimation of 10-year CVD risk‡†
Low risk (<5%)
Borderline risk (5 to 7.4%)
Intermediate risk (7.5 to 19.9%)
High risk (≥20%)

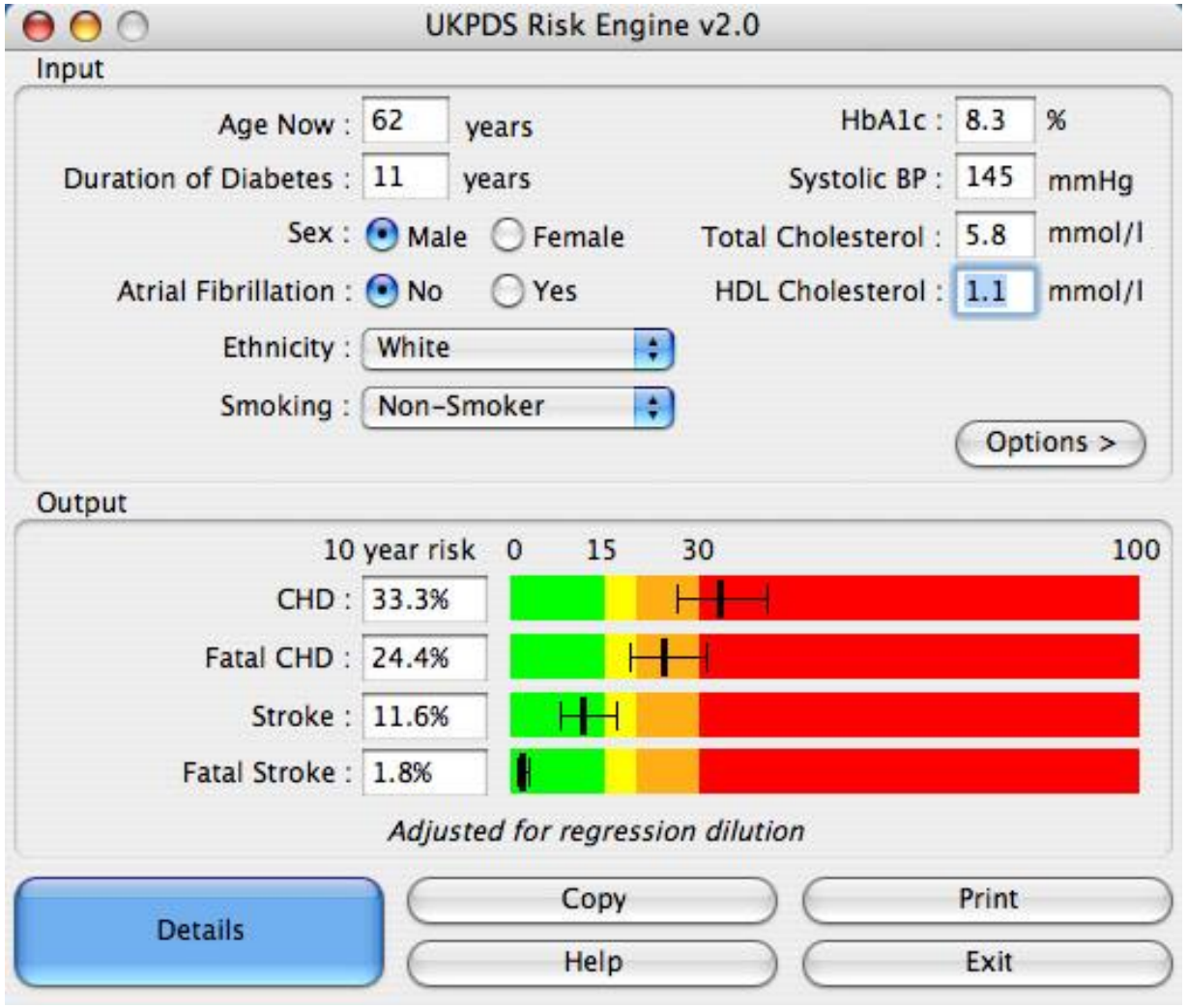
Identifying risk enhancing factors

- Family history of premature atherosclerotic CVD (men <55 years of age, women <65 years of age)
- Primary hypercholesterolemia
- Metabolic syndrome
- Chronic kidney disease with estimated glomerular filtration rate between 15 and 59 mL/min/1.73 m^2
- Chronic inflammatory conditions (eg, rheumatic diseases, HIV, etc)
- History of premature menopause before age 40 years or pregnancy associated conditions (eg, preeclampsia)
- High-risk race/ethnicities (eg, South Asian)
- Lipid abnormalities including elevated lipoprotein(a) ≥50 mg/dL (≥125 nmol/L) or elevated apoB ≥130 mg/dL
- Biomarkers including C-reactive protein (CRP) ≥2 mg/L and ankle-brachial index (ABI) <0.9

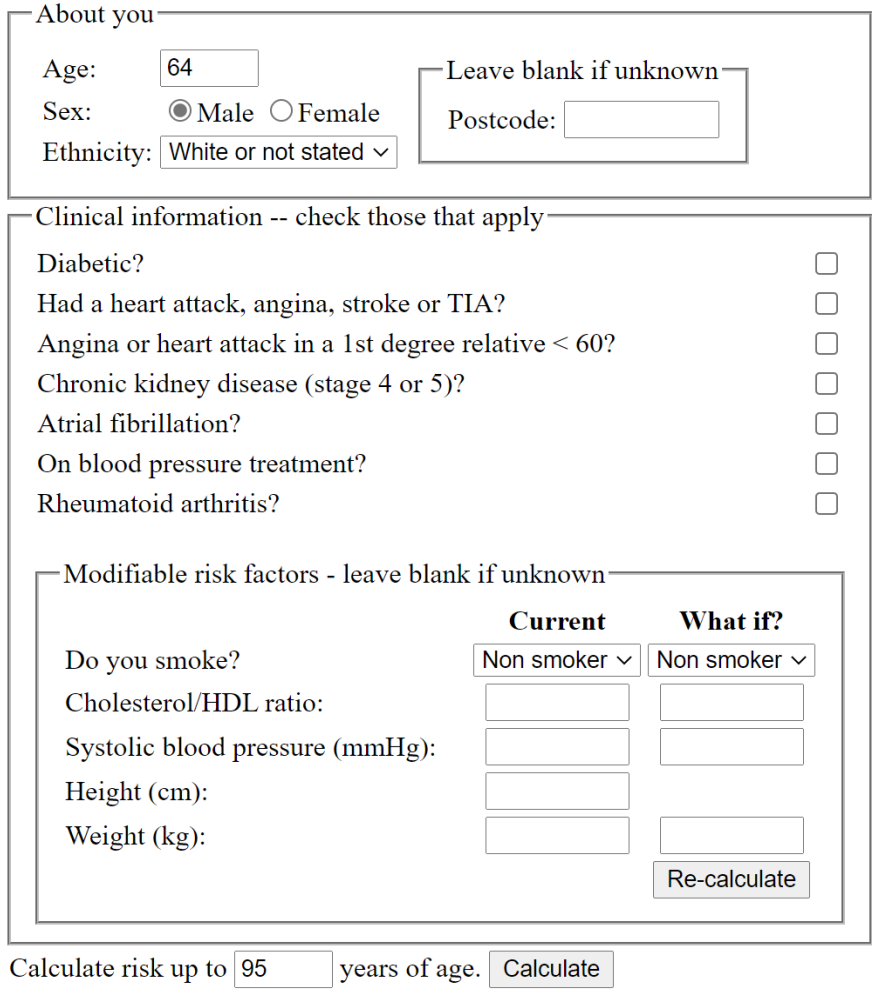
Which calculator to use ?!!

ACC/AHA risk calculator

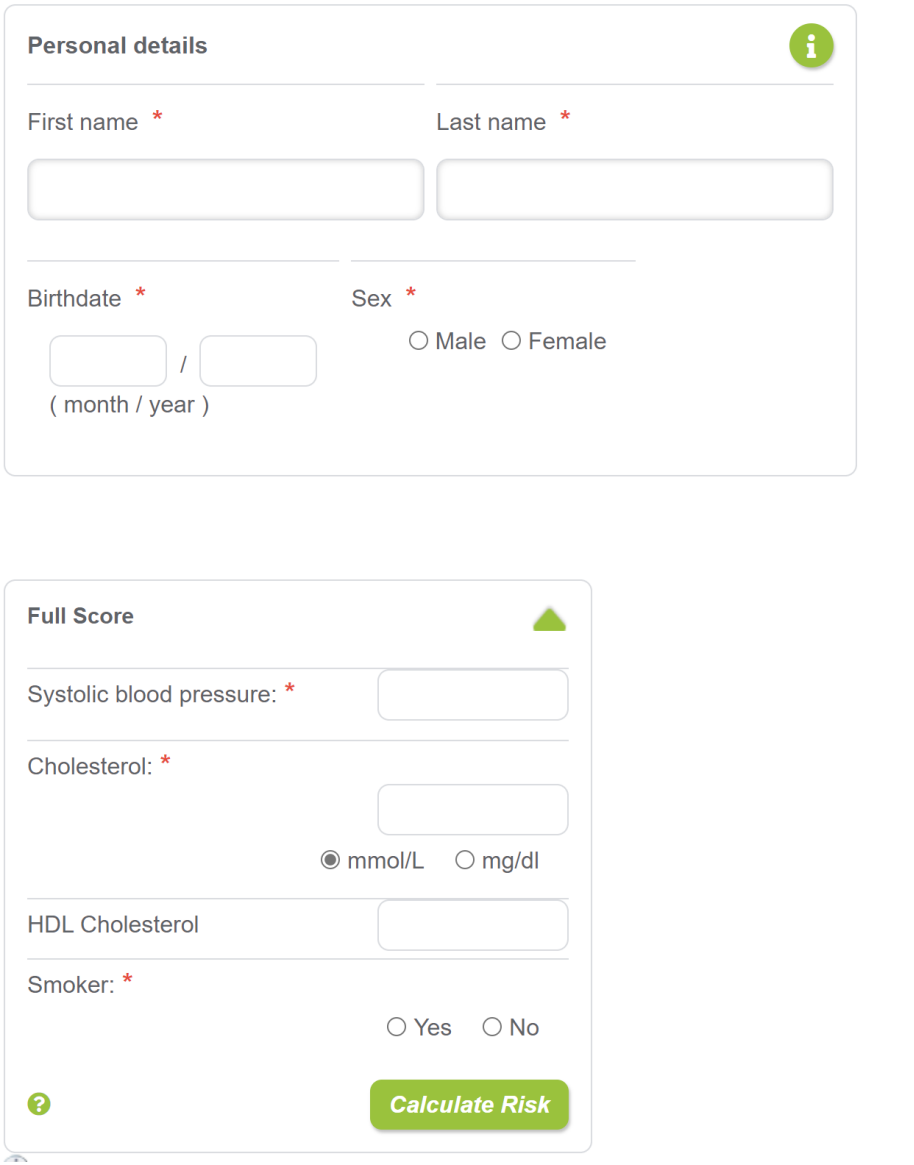
UKPDS risk calculator



The JBS3 risk calculator

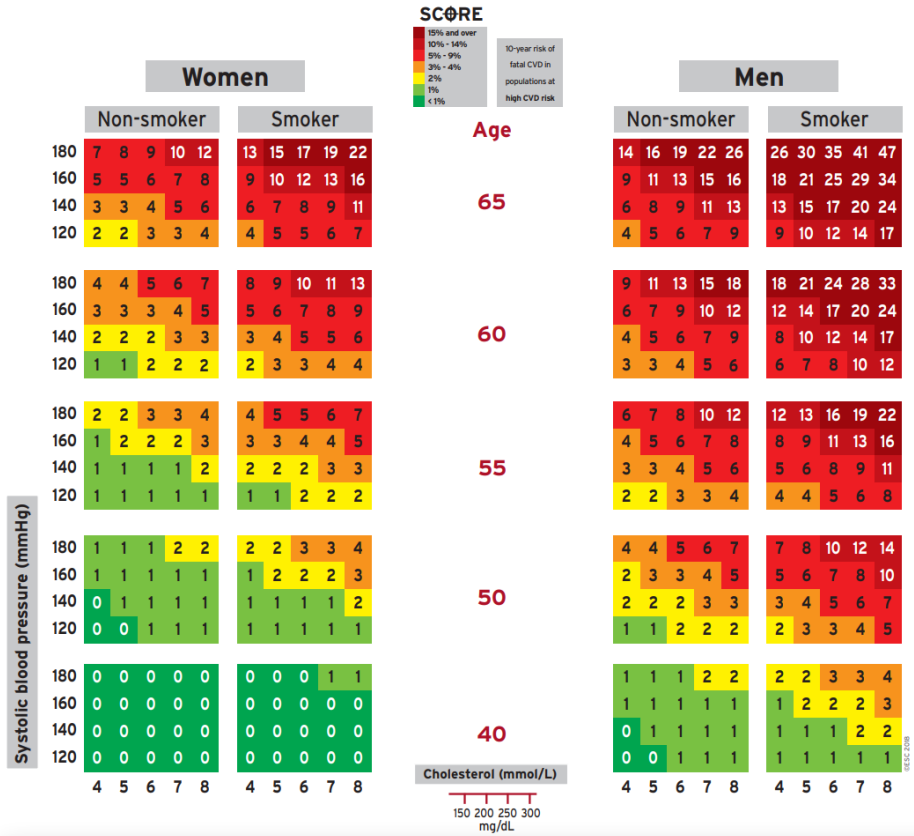


The SCORE risk calculater



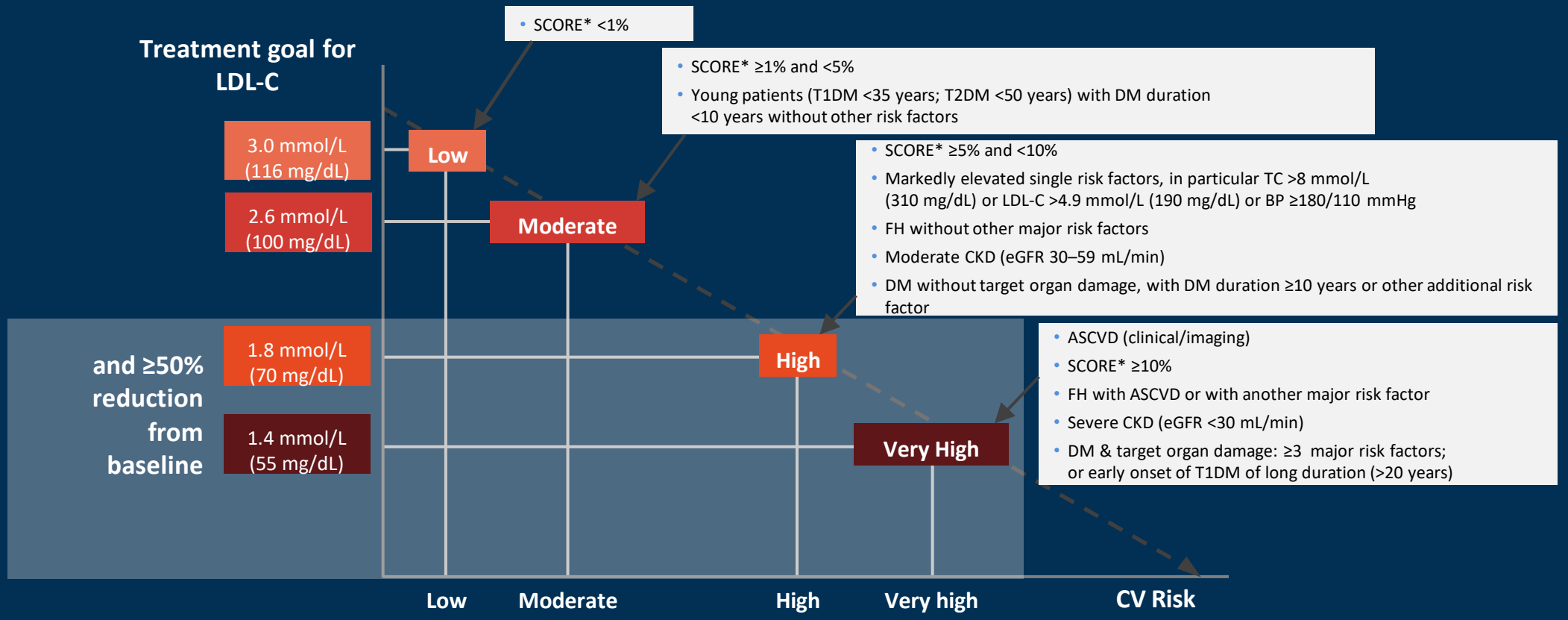
SCORE - European High Risk Chart

10 year risk of fatal CVD in high risk regions of Europe by gender, age, systolic blood pressure, total cholesterol and smoking status



LDL-C lowering is an integral part of 2019 ESC/EAS recommendations for ASCVD primary and secondary prevention

Treatment goal: LDL-C reduction of **≥50% and LDL-C <70 mg/dL** in patients at **high-risk** and LDL-C reduction of **≥50% and LDL-C <55 mg/dL** in patients with **ASCVD or very high-risk**



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

*Systematic Coronary Risk Estimation (SCORE) for 10-year risk of fatal CVD.

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

Long-term LDL-C reduction leads to proportionally greater reductions in the lifetime risk of ASCVD

Each mmol/L reduction in LDL-C reduces the relative risk of ASCVD events by:

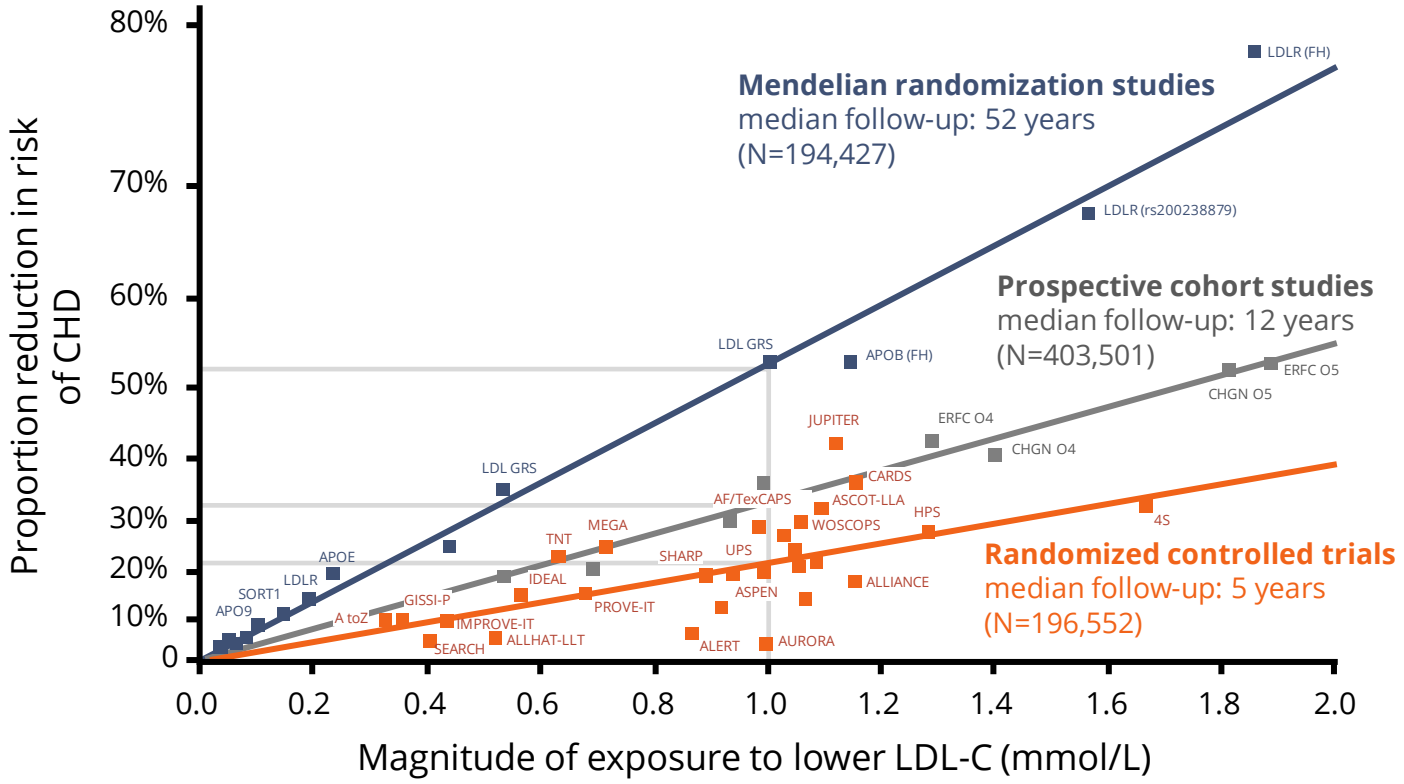
~10%

during the **first year**

~50–55%

after **40 years**

Log-linear association per unit change in LDL-C and the risk of ASCVD

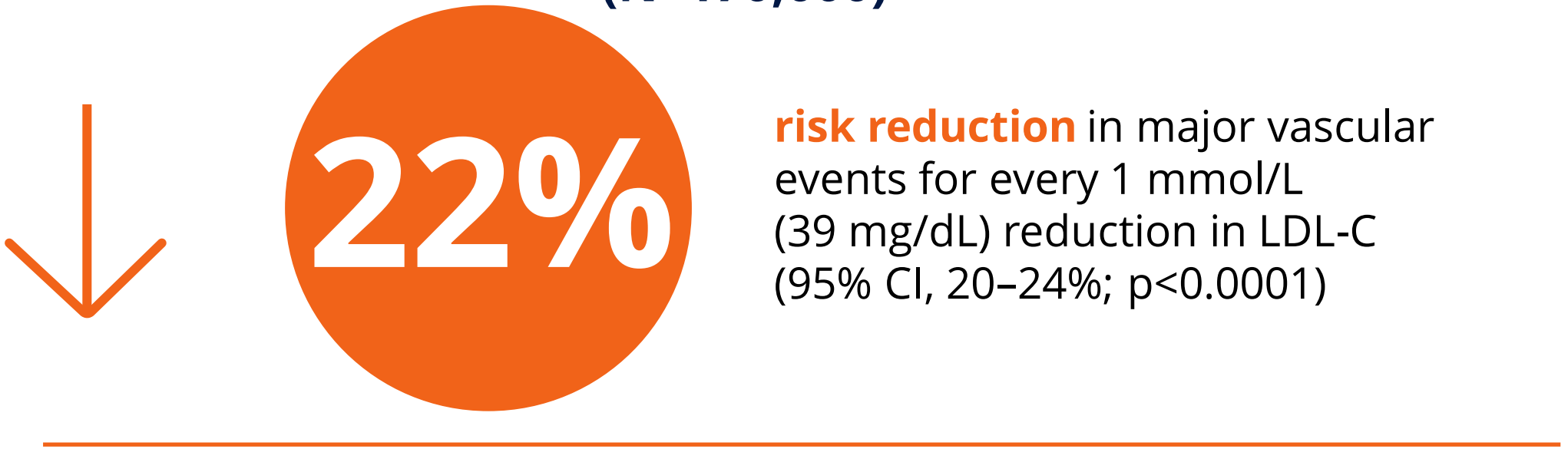


ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor.

Ference BA et al. *Eur Heart J*. 2017; 38:2459–72.

LDL-C lowering is a reliable surrogate for improving CV outcomes

Meta-analysis of 26 randomized trials of statin therapy (N=170,000)*



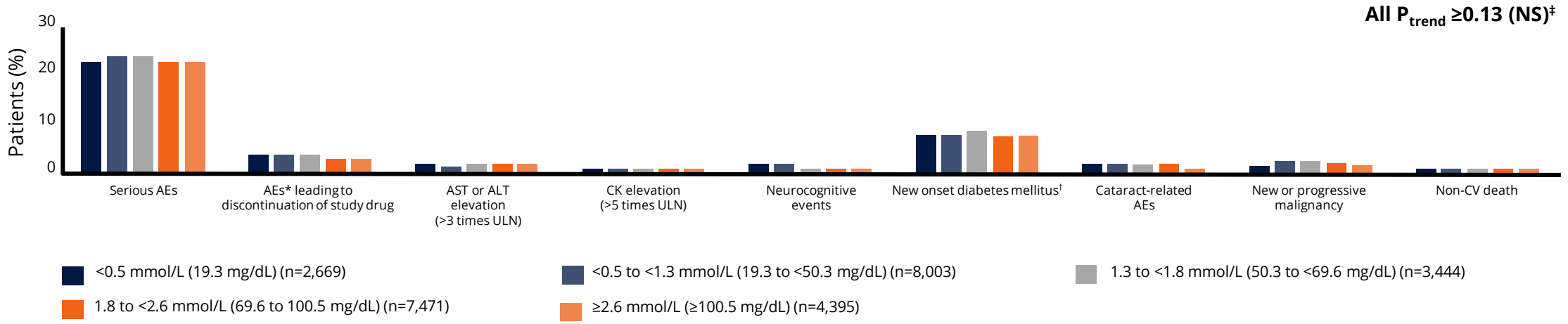
risk reduction in major vascular events for every 1 mmol/L (39 mg/dL) reduction in LDL-C (95% CI, 20–24%; p<0.0001)

*More intensive versus less intensive statin regimen (n=5) or statin versus control (n=21).
CI, confidence interval; CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol.
Cholesterol Treatment Trialists (CTT) Collaboration. *Lancet*. 2010;376:1670–81.

No significant association has been observed between very low levels of LDL-C and safety outcomes

Results from the FOURIER trial (N=25,982) showed that there were no safety concerns with very low LDL-C levels (beyond the lowest recommended current targets)[1]

Safety events by achieved LDL-C levels, over a median of 2.2 years[1]



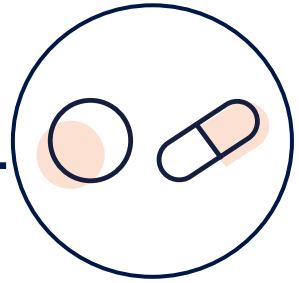
*Excludes 17 patients with injection-site reactions; †Denominator excludes patients who were diagnosed with diabetes mellitus before the Week 4 visit; ‡Adjusted for baseline characteristics.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol; NS, not significant; ULN, upper limit of normal.
1. Giugliano RP et al. *Lancet*. 2017;390:1962–71.

Many patients are unable to achieve and maintain LDL-C goals with current ASCVD therapies

DA VINCI study[1]*

Statins were the mainstay of therapy with **94% of primary prevention** patients and **94% of patients with established ASCVD** on statins

Most frequent regimen across all risk categories was **moderate-intensity statins as monotherapy**



Only **33%** of patients attained overall **2019 ESC/EAS LDL-C treatment goal**

Potential reasons for failure to achieve guideline recommended LDL-C values included:

- Lack of HCP familiarity with guidelines
- Patient reluctance to be treated with high-intensity therapies
- High cost of some medications
- Concern about statin-related AEs

*Cross-sectional study of patients receiving lipid-lowering therapies (LTT) between June 2017 and November 2018 across 18 European countries (N=5,888 [3,000 primary prevention and 2888 secondary prevention])

AE, adverse event; ASCVD, atherosclerotic cardiovascular disease; EAS, European Atherosclerosis Society; ESC, European Society of Cardiology; HCP, healthcare professional; LDL-C, low-density lipoprotein cholesterol.

1. Ray KK et al. *Eur J Prev Cardiol*. 2021;28:1279–89.

CASES

37 F

Asymptomatic

Father and parental uncle had premature CAD (3 vd at age 49)

TC 209, TG 59, HDL 64, LDL 133

After life style changes

TC 184, TG 82, HDL 50, LDL 118

ASCVD risk calculator doesn't apply but if using age 40 : 10 y risk 0.4%

Qriskscore: 0.7%

SCORE2: 1.5%

LPa : 312 nmol/l

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Meds : Pitavastatin 2, ezetimibe 10, gliclazide 120, saxagliptin 5, telmisartan 160, amlodipine 5

ASCVD : 12.9%

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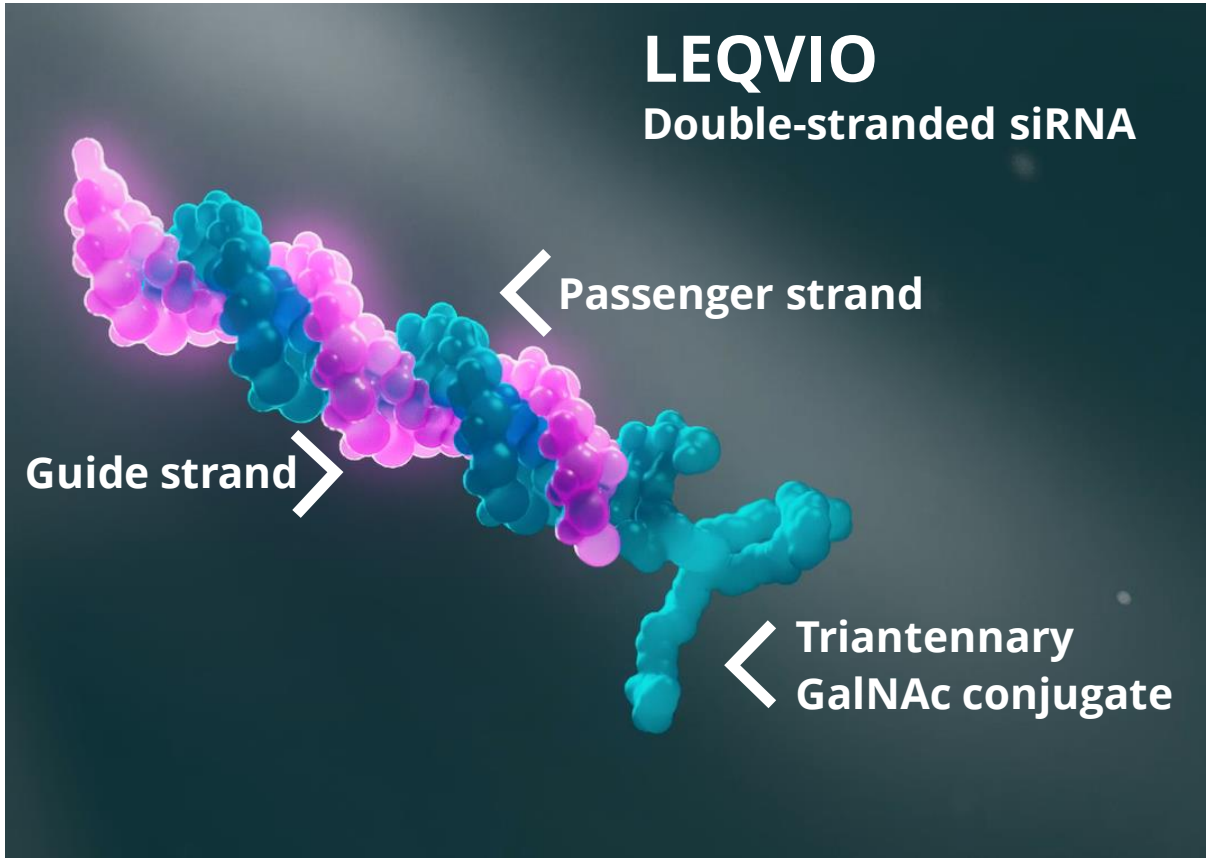
Risk score doesn't apply as patient has documented ASCVD : very high risk

LEQVIO is the first and only LDL-C–lowering siRNA therapy that selectively targets the liver



By preventing the production of the target protein (PCSK9), LEQVIO **increases hepatic uptake of circulating LDL-C**, thereby **reducing LDL-C levels in the bloodstream**[1,2]

- LEQVIO **mimics the body's natural process of RNA interference** to selectively target PCSK9 production[1,2]
- LEQVIO consists of two strands: the guide strand and the passenger strand[1,2]
  - The **passenger strand** is attached to GalNAc, which allows for targeted delivery of LEQVIO to the liver cell
  - The **guide strand** targets the mRNA by complementary base pairing and allows targeted degradation
- The target mRNA is subject to degradation in the cytoplasm and not in the nucleus[1,2]

GalNAc, N-Acetylgalactosamine; LDL-C, low-density lipoprotein cholesterol; mRNA, messenger RNA; PCSK9, proprotein convertase subtilisin/kexin type 9; RNA, ribonucleic acid; siRNA, small-interfering RNA.
1. Khvorova A. *N Engl J Med*. 2017;376:4–7; 2. Fitzgerald K, et al. *N Engl J Med*. 2017;376:41–51.

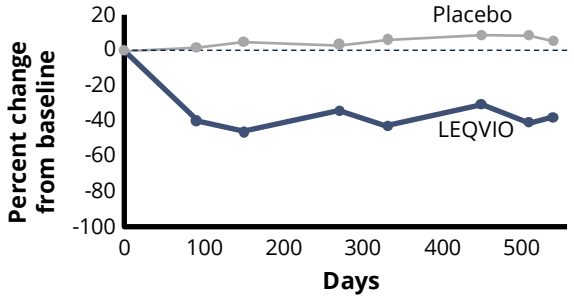
Phase 3 ORION-9, -10, and -11

LEQVIO provides effective and sustained LDL-C lowering over 18 months

Percent change in LDL-C over time

ORION-9[1]

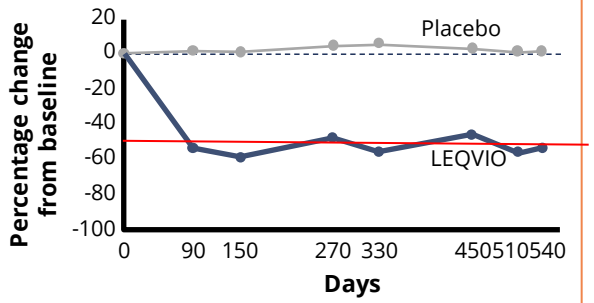
Change in LDL cholesterol



No. of patients								
Placebo	240	237	238	235	233	233	229	232
LEQVIO	242	240	239	240	237	237	231	232

ORION-10[2]

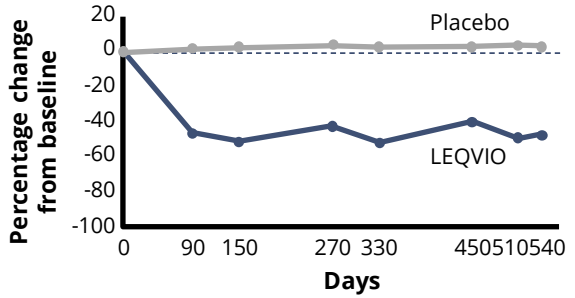
Percentage change in LDL cholesterol



No. of patients								
Placebo	780	762	745	724	715	698	666	670
LEQVIO	781	758	757	737	731	721	691	705

ORION-11[2]

Percentage change in LDL cholesterol



No. of patients								
Placebo	807	797	785	774	773	764	739	749
LEQVIO	810	790	796	778	773	768	724	742

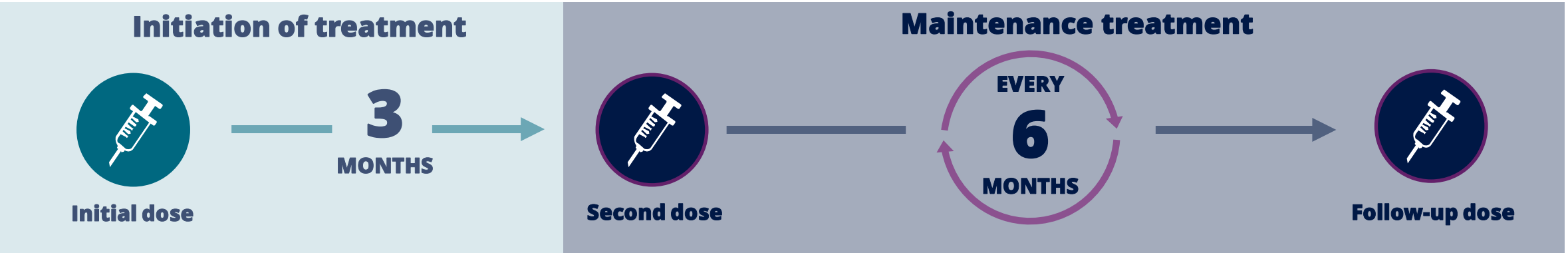
Used with permission. Raal FJ, et al. *N Engl J Med*. 2020;382(16):1520-1530.

Used with permission. Ray KK, et al. *N Engl J Med*. 2020;382(16):1507-1519.

Significant reductions in LDL-C percent change with LEQVIO vs placebo on top of maximally tolerated statin dose at Day 510 (range, -47.9% – 52.3%)

LEQVIO allows effective and sustained LDL-C lowering with two doses a year

LEQVIO is dosed initially, again at 3 months, and then once every 6 months;[1] LDL-C reduction was maintained during each 6-month dosing interval[2,3]



- Subcutaneous injection administered by a healthcare provider[1]
  - Flat-dose prefilled syringe
  - No refrigeration required
  - No pre or post injection monitoring required

- No dose adjustments for renal impairment or mild-to-moderate hepatic impairment*[1]
- The safety profile of LEQVIO was similar in patients with normal and impaired renal function[1]

- Specific uptake by the liver[1]
  - LEQVIO plasma concentrations decline within 24 hours
  - Levels are undetectable within 48 hours

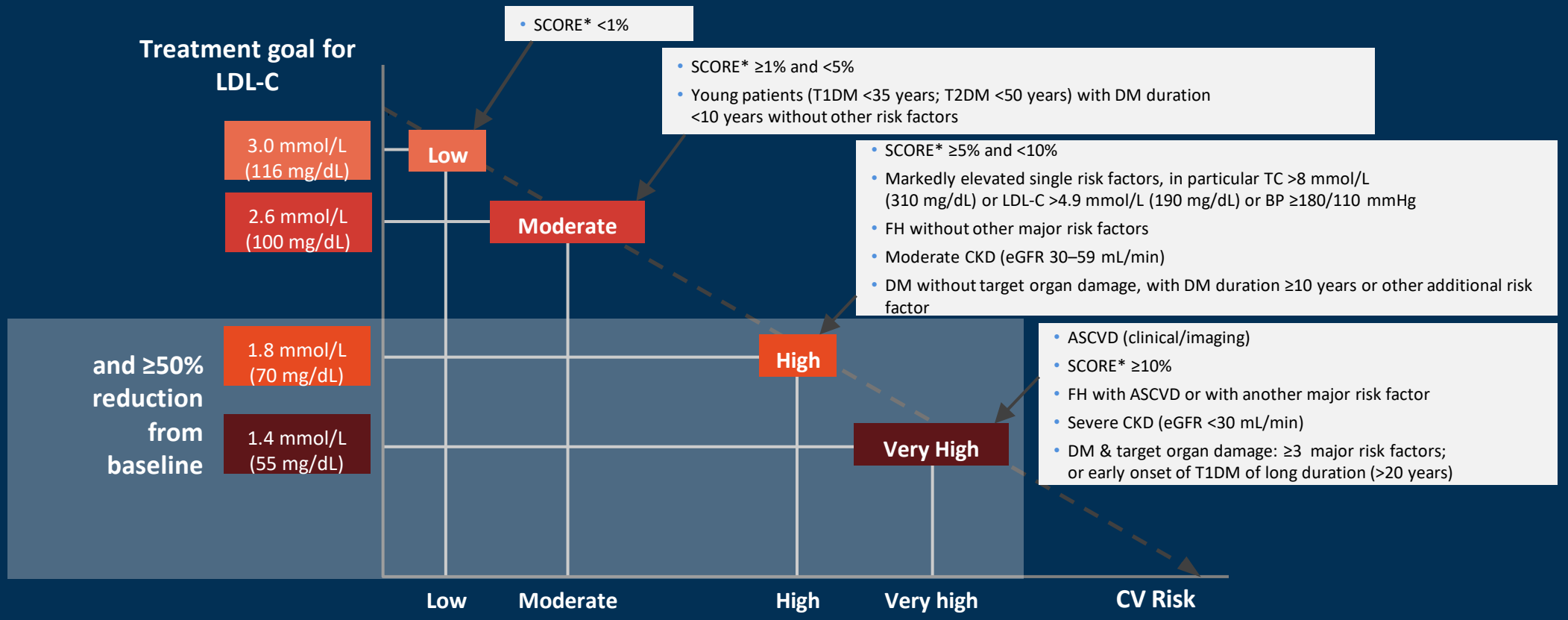
*LEQVIO should be used with caution in patients with severe renal impairment due to limited experience and in patients with severe hepatic impairment; hemodialysis should not be performed for at least 72 hours after dosing.
LDL-C, low-density lipoprotein cholesterol.

1. LEQVIO SmPC. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/leqvio [Accessed December 2021]; 2. Raal FJ, et al. *N Engl J Med*. 2020;382:1520–30; 3. Ray KK, et al. *N Engl J Med*. 2020;382:1507–19; 4. Wright RS et al. *Mayo Clin Proc*. 2020;95:77–89.

Take home message

LDL-C lowering is an integral part of 2019 ESC/EAS recommendations for ASCVD primary and secondary prevention

Treatment goal: LDL-C reduction of **≥50% and LDL-C <70 mg/dL** in patients at **high-risk** and LDL-C reduction of **≥50% and LDL-C <55 mg/dL** in patients with **ASCVD or very high-risk**



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*Systematic Coronary Risk Estimation (SCORE) for 10-year risk of fatal CVD.

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

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5. Goff DC Jr, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014; 129:S49.
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7. Graham I, Atar D, Borch-Johnsen K, et al. European guidelines on cardiovascular disease prevention in clinical practice: executive summary: Fourth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (Constituted by representatives of nine societies and by invited experts). Eur Heart J 2007; 28:2375.
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Thank you