Vascular Diseases and Therapeutics

Review Article ISSN: 2399-7400

Estimation and management of cardiovascular risk: Focus on dyslipidemia

Alejandro J Jordán-Torrent

Servicio de Cardiología, Hospital General de Alicante, Alicante 03010, Spain

Abstract

Estimation of cardiovascular risk is a need to plan prevention of atherosclerotic cardiovascular disease. Control of hyperlipidemia, besides of other cardiovascular risk factors as hypertension, diabetes, obesity, sedentarism and smoking habit, is the mainstay to lower cardiovascular events. In this review an easy method to calculate this index is shown. Drugs currently in the market are described to decrease blood levels of several lipids: low density lipoprotein cholesterol, triglycerides, lipoprotein (a), in order to reach the goals linked to the estimated risk.

Introduction

Cardiovascular disease (CVD), of which atherosclerotic CVD is the major component, is responsible for >4 million deaths in Europe each year. It kills more women (2.2 million) than men (1.8 million), although cardiovascular (CV) deaths before the age of 65 years are more common in men (490 000 *vs.*193 000) [1].

The assessment of CV risk has to take into account all known CV risk factors: Age, sex, blood pressure, smoking habit, blood cholesterol levels. Other factors, as diabetes, implies a moderate to very high risk, depending on clinical situation. Factors as obesity, physical inactivity and lipoprotein (a)(LP(a)) levels ≥ 50 mg/dL are considered as risk modifiers after overall CV risk estimation [2].

Estimation of cardiovascular risk

Currently CV risk is calculated using charts which combine risk factors considering the level of risk of countries: Low, moderate, high or very high risk (Table 1) [3]. The easiest way of doing it is opening www.heartscore.org at your country's risk and entering data. Charts combine age, sex, smoking status, systolic blood pressure and non-HDL cholesterol (Total cholesterol – HDL cholesterol). Charts are accessible in 2021 ESC Guidelines on cardiovascular disease prevention [3]. Risk figures achieved must be evaluated depending on age to know the personal level of CV risk: Low, moderate or high.

Each risk figure implies an estimation of 10-year risk of (fatal and non-fatal) CV events in that risk population. This calculation is intended for people without known CV disease. Other situations imply different levels of risk (Table 2) [2]. Diabetes mellitus (DM) in young people supposes a moderate risk, which increases to high risk when duration is ≥ 10 years or there are other risk factors and to very high risk when microangiopathy exists. An estimated glomerular filtration rate (eGFR) between 30-59 mL/min/1.73 m^2 indicates high risk level and if eGFR < 30 mL/min/1.73 m^2 (severe chronic kidney disease (CKD)) we have very high risk. Familial hypercholesterolemia means a high risk for total CV events, which increases to very high risk when another risk factor is added. All patients with known atherosclerotic CVD are at very high risk level.

Each level of CV risk implies a goal for LDL-cholesterol. These goals were stablished by the European Society of Cardiology in 2019 [4]:

1. Low risk level: LDL-Cholesterol < 116 mg/dL (Class IIb recommendation)
2. Moderate risk level: LDL-Cholesterol < 100 mg/dL (Class IIa recommendation)
3. High risk level: LDL-Cholesterol < 70 mg/dL (Class I recommendation)
4. Very high risk level: LDL-Cholesterol < 55 mg/dL (Class I recommendation)

Treatment of hypercholesterolemia

Treatment of hypercholesterolemia begins with statins. If goals are not attained, we add ezetimibe. If goals are not attained yet, we add PCSK9 inhibitors. In case of intolerance or adverse effects with statins, we can change them for bempedoic acid.

Statins

Statins competitively inhibit the HMG-CoA reductase enzyme, which synthetizes cholesterol in the liver. Then, through LDL-cholesterol receptors, liver removes cholesterol from blood to compensate the lack of synthesis, so lowering cholesterol levels in plasma. In the Cholesterol Treatment Trialist (CTT) meta-analysis [5], 26 randomized clinical trials (RCT) were analyzed, showing a reduction of 22 % of major cardiovascular events (MACE) per 1 mmol/L of LDL-cholesterol reduction. That includes CV death and total mortality.

Rhabdomyolisis is the worst side effect of statins, but is rare (1-3 cases/100 000 patient-years [6]. Myalgia is much more frequent (10-15

Correspondence to: Alejandro J Jordán-Torrent, Servicio de Cardiología, Hospital General de Alicante, Alicante 03010, Spain, E-mail: ajordant@coma.es

Keywords: *cardiovascular risk, hyperlipidemia, LDL-cholesterol, lipid-lowering therapy, triglycerides, LP(a)*

Received: October 21, 2025; **Accepted:** November 11, 2025; **Published:** November 14, 2025

Table 1. Taken from 2021 ESC guidelines on cardiovascular disease prevention in clinical practice [3]

Supplementary Table 1 Age- and sex- standardized WHO CVD mortality rates per country[1,2]

Country	Age and sex standardized CVD mortality per 100 000 person years, ICD section 9	Year collected
Low risk region		
France	70.9	2014
Israel	76.7	2015
Spain	89.4	2015
Netherlands	89.9	2016
Switzerland	90.2	2015
Denmark	90.4	2015
Norway	90.8	2015
Luxembourg	92.9	2015
Belgium	99.2	2015
United Kingdom	99.7	2015
Moderate risk region		
Iceland	101.0	2016
Portugal	107.9	2014
Sweden	109.0	2016
Italy	110.1	2015
San Marino	-	
Ireland	111.5	2014
Cyprus	111.5	2016
Finland	128.5	2015
Austria	130.9	2016
Malta	133.3	2015
Greece	138.8	2015
Germany	139.0	2015
Slovenia	143.3	2015
High risk region		
Albania	184.5	2010
Czech Republic	195.0	2016
Turkey	199.5	2015
Kazakhstan	214.0	2015
Croatia	214.6	2016
Poland	223.8	2015
Estonia	234.8	2015
Slovakia	239.2	2014
Hungary	274.1	2016
Bosnia and Herzegovina	279.2	2014
Very high risk region		
Armenia	306.3	2016
Lithuania	309.0	2016
Georgia	309.6	2015
Latvia	327.2	2015
Serbia	329.1	2015
Romania	330.5	2016

Continued

Supplementary Table 1 *Continued*

Country	Age and sex standardized CVD mortality per 100 000 person years, ICD section 9	Year collected
Montenegro	348.4	2009
Russian Federation	368.8	2015
TFYR Macedonia	387.8	2013
Belarus	395.4	2014
Azerbaijan	416.5	2007
Bulgaria	421.2	2014
Republic of Moldova	442.2	2016
Ukraine	476.7	2015
Kyrgyzstan	476.9	2015
Uzbekistan	478.6	2014
Egypt	543.7	2015
Morocco	-	-
Syria	-	-
Tunisia	-	-
Lebanon	-	-
Algeria	-	-
Libya	-	-

ICD = International Classification of Diseases. Red: very high risk; orange: high risk, yellow: moderate risk; green: low risk. Countries without available population or incidence data in the WHO database (indicated by -) were grouped using rates available from neighbouring countries.

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%) [7], and can compel us to change or stop treatment. Pitavastatin may be an alternative, or bempedoic acid too.

Cholesterol absortion inhibitors

Ezetimibe inhibits absortion of dietary cholesterol at small bowel endothelium, by interacting with the Niemann-Pick C1-like protein 1, without affecting the absortion of fat-soluble nutrients. This decreases the offer of cholesterol to the liver, which enhances the uptake of blood cholesterol through LDL-receptors, so lowering cholesterol levels in plasma. Ezetimibe alone reduces LDL-cholesterol levels by 18 % [8], and when added to statin therapy, reduction attains around 20 % more, if we compare with the effect of statin alone [9]. The association of simvastatin plus ezetimibe has proved a reduction in MACE (IMPROVE-IT trial) [10].

Bempedoic acid

Bempedoic acid inhibits the enzyme ATP-citrate lyase, which acts before HMG-CoA reductase does, as statins do, in cholesterol synthesis. This drug decreases LDL -cholesterol by 18% [11], and combined with ezetimibe the reduction reaches 38% [12]. The CLEAR study showed a 13% reduction in MACE *vs.* placebo in statin intolerant patients treated with bempedoic acid. Muscle side effects of bempedoic acid were comparable to placebo [13]. This allows its use when statins are not tolerated.

Proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9 inh)

PCSK9 controls the expression of hepatic LDL receptors. PCSK9 inhibition increases the number and action of LDL receptors, which remove cholesterol from blood, so lowering its levels. There are two drugs in the market, both monoclonal antibodies: evelocumab and alirocumab. These drugs decrease LDL-cholesterol levels by 46%-73% when combined with statins [14]. They are administered subcutaneously every two weeks, and act through LDL-receptors; that's why they have little effect in patients with homocigous familial hypercholesterolemia (HoFH). However, they slightly lower LPa. FOURIER [15], a RCT with evelocumav, randomized patients with atherosclerotic CVD (coronary artery disease, peripheral arterial disease or stroke), and got a decrease of 15% in MACE. ODYSSEY [16], a RCT with alirocumab in patients after a recent acute coronary syndrome, got same benefit, but included an all-cause mortality reduction.

Inclisiran is an interfering RNA molecule which inhibits the synthesis of PCSK9. It's administered subcutaneously every 6 months, and lowers LDL-cholesterol by around 50% [17]. It's ability to decrease MACE is being studied in two phase III RCT which are currently ongoing.

There's another research molecule, VERVE-102, which inhibits the gene related to the synthesis of PCSK9. An open-label, fase 1b, single ascending dose study (VT-10201) is currently ongoing to evaluate the safety of this drug (NCT 06164730).

Drugs for homocigous familial hypercholesterolemia

Lomitapide: Lomitapide is an inhibitor of the microsomal triglyceride transfer protein, so inhibiting the formation of VLDL in the liver and chylomicrons in the intestine. This drug is intended for HoFH patients, in combination with statins, since they don't respond to other therapies. In a titration study lomitapide reduced LDL-cholesterol by 44% in this population [18]. There are no studies on CV outcomes with this drug.

Mipomersen: Mipomersen is an oligonucleotide which binds to the mRNA of ApoB-100, reducing the production of LDL and LPa, and is indicated in HoFH too, but is not approved by the European Medicines Agency.

Table 2. Taken from 2025 focused update of the 2019 ESC/EAS guidelines for the management of dyslipidaemias [2]

Very high risk	People with any of the following: • Documented ASCVD, either clinical or unequivocal on imaging. Documented ASCVD includes previous ACS (MI or unstable angina), chronic coronary syndromes, coronary revascularization (PCI, CABG, and other arterial revascularization procedures), stroke and TIA, and peripheral arterial disease. Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque[a] on coronary angiography or CT scan or on carotid or femoral ultrasound or markedly elevated CAC score by CT[b] • DM with target organ damage,[c] or at least three major risk factors, or early onset of T1DM of long duration (>20 years) • Severe CKD (eGFR <30 mL/min/1.73 m^2) • A calculated SCORE2 or SCORE2-OP ≥20% for 10 year risk of fatal or non-fatal CVD • FH with ASCVD or with another major risk factor
High risk	People with any of the following: • Markedly elevated single risk factors, in particular TC >8 mmol/L (>310 mg/dL), LDL-C >4.9 mmol/L (>190 mg/dL), or BP ≥180/110 mmHg • Patients with FH without other major risk factors • Patients with DM without target organ damage,[c] with DM duration ≥10 years or another additional risk factor • Moderate CKD (eGFR 30–59 mL/min/1.73 m^2) • A calculated SCORE2 or SCORE2-OP ≥10% and <20% for 10 year risk of fatal or non-fatal CVD
Moderate risk	People with any of the following: • Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors • Calculated SCORE2 or SCORE2-OP ≥2% and <10% for 10 year risk of fatal or non-fatal CVD
Low risk	• Calculated SCORE2 or SCORE2-OP <2% for 10 year risk of fatal or non-fatal CVD

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ASCVD, atherosclerotic cardiovascular disease; ACS, acute coronary syndromes; BP, blood pressure; CABG, coronary artery bypass graft surgery; CAC, coronary artery calcium; CKD, chronic kidney disease; CT, computed tomography; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; FH, familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PCI, percutaneous coronary intervention; SCORE2, Systematic Coronary Risk Evaluation 2; SCORE2-OP, Systematic Coronary Risk Evaluation 2-Older Persons; T1DM, type 1 DM; T2DM, type 2 DM; TC, total cholesterol; TIA, transient ischaemic attack.

[a]Typically defined by >50% stenosis.

[b]e.g. CAC score >300.

[c]Target organ damage is defined as microalbuminuria, retinopathy, or neuropathy.

Evanicumab: Evanicumab is a monoclonal antibody against angiopoietin-like 3 which has shown reductions of LDL-cholesterol around 50% in these patients [19].

Drugs to raise HDL-cholesterol

Molecules as evacetrapib or anacetrapib (cholesteryl ester transfer protein inhibitors) increase > 100% HDL levels with no or slightly decrease of LDL levels, but have no proved beneficial effects on MACE, and are not in the market.

Treatment of hypertriglyceridemia

Fibrates

These drugs are agonists of peroxisome proliferator-activated receptor α (PPAR-α), lowering trygliceride (TG) levels around 50% and LDL-cholesterol < 20% [20]. Fibrates have not shown a decrease in MACE in RCT. They can be used (better fenofibrate) added to statins to reduce TG > 200 mg/dL in high risk patients with controlled LDL-cholesterol levels (IIb recommendation) [21].

OMEGA-3 polyunsaturated fatty acids (PUFA)

These fatty acids seem to interact also with PPAR-α, decreasing TG levels up to 25% [22]. REDUCE-IT trial [23], evidenced a decrease in MACE in high risk patients on statins with LDL-levels < 100 mg/dL and TG levels > 150 mg/dL. PUFA used was icosapent ethyl. However, in another study (STRENGTH [24]) there was not a significant effect on MACE, perhaps because of the different PUFA employed: Combined eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Current recommendation (IIa) is to use high dose icosapent ethyl in addition to statins in high risk patients with TG > 150 mg/dL[2]).

Antisense oligonucleotides

***Volanesorsen*:** Volanesorsen is an antisense oligonucleotide targeting ApoC-III mRNA, which lowers TG by 70%, evidenced in the COMPASS study [25], which randomized patients with TG > 500 mg/dL, including patients with familial chylomicronemia syndrome (FCS). A reduction in pancreatitis has been demonstrated in a meta-analysis [26]. This drug is currently approved to treat FCS when other drugs and diet had failed, and there's high risk of pancreatitis (IIa recommendation)[2].

***Olezarsen*:** Olezarsen is another antisense oligonucleotide which inhibits ApoC-III, reducing TG levels by 60% (Essence–TIMI 73b trial [27]), but there's no information on MACE or reduction of pancreatitis.

Treatment of elevated Lp(a) levels

LP(a) is the covalent union of a LDL lipoprotein with a glycoprotein, apolipoprotein (a) (apo(a)) [28]. Its levels depend mainly on genetics (90%) [29]. LP(a) levels > 50 mg/dL are associated with a rise of atherosclerotic CVD and aortic valve stenosis incidences [30]. At the moment, there are no approved treatments to lower this lipoprotein. Since high levels of LP(a) implies higher CV risk, they should be considered a risk-modifying factor, underscoring the need for strong treatment of other risk factors,i.e. hypercholesterolemia. Some natural products, as l-carnitine, coenzyme Q 10, and xuezhikang, have shown the ability to decrease LP(a) levels [31]. However, there are no studies so far linking a decrease of LP(a) levels with a reduction of MACE. Muvalaplin, [32] an oral small molecule inhibitor of LP (a) hepatic synthesis, and zerlasiran [33], a small interfering RNA , have demonstrated decreases of 80%-90% of LP(a) levels in phase 2 RCT.

Conclusion

Estimation of cardiovascular risk is essential to plan prevention strategies for atherosclerotic cardiovascular disease. Control of hyperlipidemia remains a cornerstone of risk reduction. The growing array of lipid-lowering therapies enables personalized management to achieve lipid targets and lower cardiovascular events according to individual risk.

Conflicts of interest

The author declares no conflict of interest.

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