

Highlight on earlier concepts on which today's guidelines are based

Update in antilipidaemic management of atherosclerotic cardiovascular disease: emerging concepts, new risk assessment, and risk-related management

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Introduction

The first publication by WB Kannel et al. from the Framingham study on the causal role of hypercholesterolaemia in myocardial infarction dates back exactly 60 years [1]. The subsequent increasing awareness of hypercholesterolaemia and of “classical” cardiovascular risk factors (arterial hypertension, diabetes and tobacco consumption) conveyed by the medical communities and by numerous national and global health campaigns, were determinant for the decrease of the cardiovascular mortality curve in western countries between the 1970s and 80s. This was concomitant with the rapidly increasing body of knowledge on the molecular pathophysiological mechanisms of dyslipidaemia, i.e. the pivotal role of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase as the rate controlling enzyme of the mevalonate pathway [2], and to the discovery of the first statins – a gift from nature, as Akira Endo used to call it [3]. During the 80s and 90s the concept and causality of serum low-density lipoprotein (LDL) cholesterol as a major cause of coronary artery disease emerged thanks to numerous prospective randomised and cohort trials in secondary and primary prevention with statins [4], confirming the concept “lower is better”. On the brink of the millennium new scenarios created by scientists during the preceding decades allowed a better insight into the biomolecular and genetic processes, the most important of the latter being the sequencing of the full human genome. The unanticipated power of gathering immense amounts of data has enlarged our understanding, opening the way also to new therapeutic strategies. The goals of this review are to highlight the

concepts emerging in the early 2000s, which constitute the backbone of both the 2019 European society of Cardiology (ESC) guidelines on dyslipidaemia and of the very recent 2021 ESC clinical practice guidelines on cardiovascular disease prevention [5, 6].

Atherosclerotic cardiovascular disease

During the early 1990s the terminology of Athero-Scle-rotic Cardio-Vascular Disease (ASCVD) has been increasingly used, implicitly recognising that not only coronary events matter, but the whole arterial vascular tree has to be considered when investigating and managing atherosclerosis. This was emphasised by the seminal world-wide REACH registry data indicating how the whole atherosclerotic vascular burden, including cerebral arteries, the whole aorta and the lower extremity arteries (non-coronary artery atherosclerosis) is a major determinant of the prognosis for the single patient or subject at risk [7, 8].

Thus, the acronym “ASCVD” has entered not only into the familiar medical acronyms in everyday practice, but also into selected cardiovascular risk calculators such those used and proposed by the American Heart Association (AHA) / American College of Cardiology (ACC) and ESC.

Atherosclerotic plaque burden: the role of new imaging techniques

Longitudinal studies implementing new imaging techniques such as intravascular ultrasound (IVUS) and magnetic resonance imaging (MRI) of plaques [9, 10] have contributed to corroborating the pivotal role that

reduction of LDL cholesterol plays in reducing progression, and for the first time – using coronary IVUS – demonstrated regression of plaque volume, which started at a serum LDL cholesterol level below 1.6 mmol/l. In addition, no threshold level below which the benefit of LDL cholesterol lowering ceases could be established. Further studies also proved that combination therapy (adding ezetimibe or proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitors) [11] may have additional protective cardiovascular effects, reducing disease progression and improving prognosis in selected patients [11, 12].

Several studies have recently also shown how imaging of atherosclerotic plaques by ultrasound at the level of the carotid and femoral arteries may represent a potential tool for risk reclassification, thus potentially redefining prevention strategies in selected patients (ESC guidelines indication level IIA) [13, 14].

Cumulative exposure to LDL burden

“The lower and the earlier is better”

An important recent achievement in the field of human genetics has been the introduction in recent years of the so-called Mendelian randomisation studies, which have overcome the challenge of both reversal and causality of dyslipidaemia for ASCVD. In analogy to randomised clinical trials where patients/subjects are randomised to either placebo or active drug, in Mendelian randomised studies patients/subjects are randomly assigned either as carriers or non-carriers of a specific gene variant. This allows a virtually time-un-

limited observation of a genetic mutation and its life-long effects. Thus, randomised Mendelian studies have been instrumental in confirming the importance of cumulative exposure to the LDL burden. A comparison among three large meta-analyses of randomised clinical trials, cohort studies, and Mendelian randomised studies including >20 million person-years of follow-up, and >150,000 cardiovascular events, has shown how the proportional risk reduction of coronary artery disease per cumulative reduction of exposure of 1 mmol/l serum LDL cholesterol increases from 22% for the randomised controlled trials (mean follow-up 5 years), to 33% for cohort studies (mean follow-up 12 years), and up to 52% for randomised Mendelian meta-analysis (mean follow-up 53 years). This is a further piece of evidence that not only the absolute reduction in serum LDL cholesterol level but – most importantly – the reduction of cumulative time-related exposure to the LDL burden is associated with reduction of atherosclerotic cardiovascular diseases [4, 15]. This has been labelled with the expression “the earlier and the longer is better.” In order to highlight this concept, a few authors have proposed the use of terms such as “LDL-years” or “cholesterol-years”, in analogy to “pack-years”, a familiar concept for assessing prolonged time-related exposure to a noxious agent.

Cardiovascular risk assessment and risk-related drug therapy

Very high-risk and high-risk patients

Assessment of cardiovascular risk is recommended by all guidelines on prevention of ASCVD. Patients with a history of previous manifest coronary artery disease have been always considered at higher risk and thus suitable for more aggressive prevention strategies (i.e., secondary prevention). One of the most important novelties introduced in the 2016 and 2019 ESC guidelines [5, 6, 16] has been the introduction of a so called “very high-risk” category (table 1), which includes all the patients with overt clinical cardiovascular disease as well as all those with risk equivalents. This group includes subjects with significant unequivocal ASCVD on imaging, a markedly elevated single risk factor (LDL cholesterol serum level >4.9 mmol/l, blood pressure >180/100 mm Hg), diabetes mellitus with target organ damage, moderate-to-severe chronic kidney disease, and with familial hyperlipidaemia. Table 1 shows the characteristics of the patients at “very high risk” and “high risk”. Indeed, these two groups of patients do not even need to undergo risk assessment by risk calculator used for apparently healthy subjects such as the ESC SCORE2 calculator.

Very high risk and high risk Cardiovascular categories (as defined in the 2019 ESC guidelines on dyslipidemia)	
Very-high risk	
Documented ASCVD	
- clinical	. stable angina, coronary revascularization (PCI, CABG, and other arterial revascularization procedures), stroke and TIA, and peripheral arterial disease.
- Unequivocally documented ASCVD on imaging known to be predictive of clinical events	significant plaque on coronary angiography or CT scan (multivessel coronary disease with two major epicardial arteries having >50% stenosis) or on carotid ultrasound.
- DM	. with target organ damage, 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 SCORE	. ≥ 10% for 10-year risk of fatal CVD
- FH	. with ASCVD or with another major risk factor.
High-risk	
- Markedly elevated single risk factors	. in particular TC, >8 mmol/L (>310 mg/dL) . LDL-C > 4.9 mmol/L (>190 mg/dL) . BP ≥180/110 mmHg.
- FH without other major risk factors.	. without other major risk factors.
- DM without target organ damage	. duration ≥ 10 years or another additional risk factor.
- Moderate CKD	. eGFR 30-59 mL/min/1.73 m ²
A calculated SCORE	. ≥ 5% and <10% for 10-year risk of fatal CVD

Table 1: Very high-risk and high-risk cardiovascular categories.

SCORE2 risk prediction algorithms

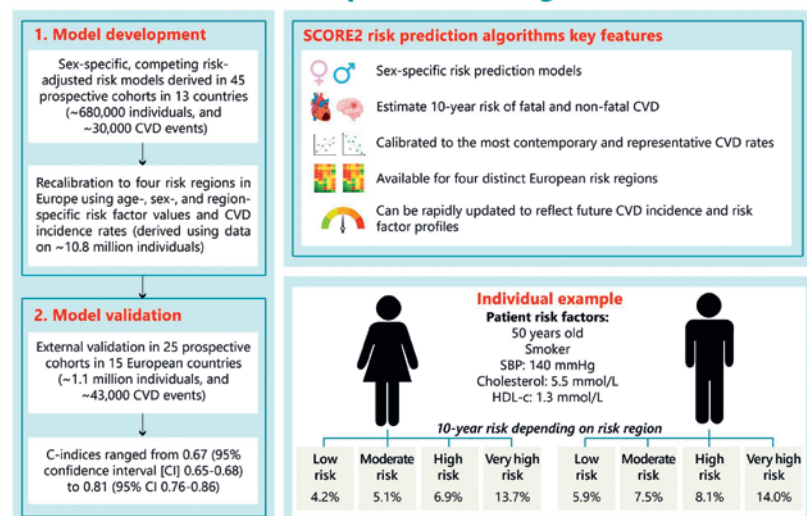


Figure 1: SCORE2 risk prediction algorithm. Development process, key features and illustrative example of the SCORE2 risk prediction algorithms for European populations. Image reprinted with permission from European Heart Journal. 2021;42:2439–2454.

Very high-risk and high-risk patients deserve an aggressive prevention strategy. The guidelines recommend that very high-risk patients (in both primary and secondary prevention) should achieve a goal LDL cholesterol level of <1.4 mmol/l and at least 50% reduction from baseline LDL cholesterol levels. In high-risk patients, the LDL cholesterol goal is <1.8 mmol/l and at least 50% reduction from baseline levels. These goals reinforce the view that the lower the LDL cholesterol level, the better for prevention of cardiovascular outcomes in these very high-risk patients. These thresholds also encompassed the LDL cholesterol value that has been demonstrated in vivo by IVUS to reduce coronary plaque burden.

Acute coronary syndrome patients are at very high risk of recurrent events. In the case of recurrence within two years, an LDL cholesterol goal of <1.0 mmol/l may be considered.

SCORE2/SCORE2-OP: a change paradigm

The ability to collect a huge amount of data from a steadily increasing number of randomised controlled trials, cohort studies and registries, and the possibility through a joint effort by epidemiologists, computer scientists and statisticians to merge this very large scale information, allows risk assessment to be better defined. This has been the case for the major effort by the SCORE2 ESC working group who recently presented the new SCORE2 and SCORE2-OP (where “OP” means “Older Persons”) risk prediction algorithm [17]. SCORE2 was defined on derivation models including 24 cohorts studies involving more than 600,000 individuals and over 30,000 cardiovascular events recalibrated and re-

ferred to four topographic macro-areas at incremental risk in Europe (low-, moderate-, high-, and very high-cardiovascular disease risk). External validation was achieved from 25 cohorts including more than 1,000,000 individuals from 15 countries with more than 40,000 cardiovascular events (fig. 1).

These recently revised calculators have been designed to improve risk prediction and to replace the previous outdated ESC SCORE. The SCORE2/OP calculator is available and downloadable on the internet (<https://www.escardio.org/Education/ESC-Prevention-of-CVD-Programme/Risk-assessment/esc-cvd-risk-calculation-app>) and is also presented in the form of new ESC SCORE2/SCORE2-OP charts referring to the four area of specific risk (where Switzerland belongs to a low-risk area). The following important factors specific to the new SCORE2 and SCORE2-OP merit emphasis. Firstly, the new calculator estimates 10-year risk for both fatal and non-fatal cardiovascular events, including stroke and myocardial infarction and not mortality only. Secondly, treatment thresholds based on risk estimation were defined separately for three age groups, less than 50 years old and 50 to 69 (SCORE2), which allow more specific risk estimation than with cardiovascular years old, and 70 or more years (SCORE2OP), in order to avoid undertreatment in the young and to avoid overtreatment in older persons [18] while also incorporating the concept of the life-long risk. As a result, for younger

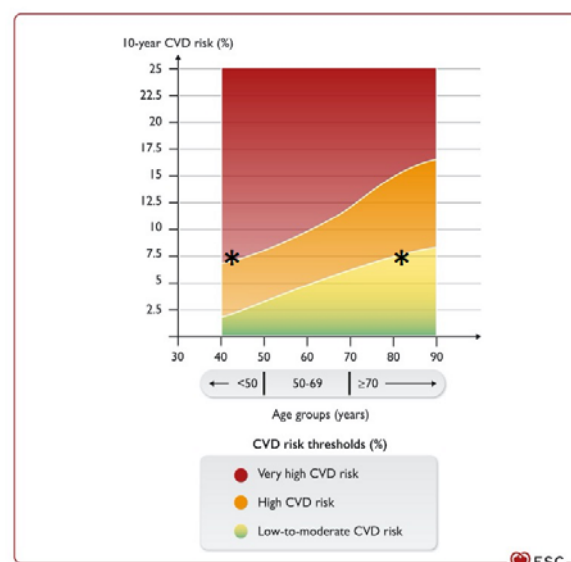


Figure 2: Schematic representation of increasing 10-year cardiovascular disease risk reduction thresholds across age groups. Schematic representation of increasing 10-year CVD risk reduction thresholds across age groups. The two asterisks (*) show how 8% for a 42-year-old person will be considered as very high risk, whereas for a 82-year-old person the same value (8%) will correspond to a low-to-moderate risk. Image reprinted with permission from European Heart Journal. 2021;42:2439–2454.

adults, treatment thresholds are lower than for older adults (fig. 2).

Thus, SCORE2 takes into account duration of exposure to a risk factor (LDL years) and the benefit of lifelong risk factor treatment for younger people.

Conversely, the specific calculator for older populations (SCORE-OP: >70 years) should avoid risk overestimation occurring with the use of the former SCORE risk algorithm. Third, in order to take into account all atherogenic lipoproteins, instead of LDL-, the non-HDL cholesterol level was chosen for risk calculation in SCORE2 and SCORE-OP

Anti-lipidaemic strategies

For determination of the adequate drug regimen and drug intensity in the individual patient or apparently healthy subject, the ESC guidelines advise proceeding as follow. Firstly, one needs to start with estimation of the risk and the corresponding target LDL cholesterol level according to the SCORE2/SCORE2OP calculator or chart. Then calculate the absolute and percentage reduction in LDL cholesterol needed to diminish the risk by subtracting the target LDL cholesterol level from the baseline level. In order to identify the most appropriate single drug, drug combination and intensity of treatment refer to table 2, which shows the anticipated mean percent LDL cholesterol reduction obtained with different drug regimens.

A detailed review of antilipidaemic drugs is beyond the scope of this review and thus just a very brief description of the distinct drug compounds is given below (and under the key points).

Table 2: Estimated LDL cholesterol lowering potency*.

DRUG TYPE	LDL-REDUCTION (%)
STATINS	
High intensity	>50
Moderate intensity	30–50
Low intensity	<30
EZETIMIBE	20–25
EZETIMIBE + STATIN	65
PCSK9 inhibitor	40–60
Hig- intensity statin	75
Ezetimibe	85
INCLISIRAN	50
BEMOEDOIC ACID	
Alone	21
Combined with	28

References: Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APHA/ASPC/NLA/PCNA guidelines on the Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2019;73:3168–3209
Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias:lipid modification to reduce cardiovascular risk ESC Scientific Document Group. *Eur Heart J.* 2020;41:111–188.

The well known effect of statins on inhibition of HMG-CoA reductase induces an enhanced expression of the LDL receptor on hepatic cells, favouring clearance of LDL from the blood stream. High-dose statins with a mean serum LDL reduction of 50% remain the primary pharmacotherapy used to lower LDL cholesterol levels with relative reductions in cardiovascular events and all-cause mortality of 22% and 10% per each 1 mmol serum LDL cholesterol reduction, respectively (19).

The successful introduction of ezetimibe, a compound that blocks the Niemann–Pick C1-like 1 cholesterol transfer protein preventing intestinal biliary cholesterol reabsorption [20], confirmed the concept “the lower the better”, and reduced for the first time the barrier of the residual cholesterol risk beyond statins. This encouraged the development of further LDL-reducing drugs, namely the PCSK9 inhibitors (evolucumab and arilucumab). The PCSK9 enzyme attaches to the LDL receptor and induces its degradation within the hepatic cell. Subcutaneously injected anti-PCSK9 monoclonal antibodies deactivate the PCSK9 enzyme, enhancing the number of disposable LDL receptors on the hepatic surface, thus diminishing circulating LDL cholesterol. In the two seminal randomised clinical trials, Fourrier and Odyssey, subcutaneous treatment with evolucumab, and alirocumab reduced by almost 60% the serum LDL, which was associated by a 15% reduction of the major combined clinical endpoint [21, 22]. These results probably underestimate the potential clinical effect of these drugs, partly because of the too short follow-up as postulated by Gencer and Mach [23]. The same probably holds true for inclisiran, an interfering RNA that targets hepatic synthesis of PCSK9 [24]. The non-oral systemic delivery of these drugs, on top of their additive antilipidaemic efficacy, constitutes a change of paradigm not only in treating residual hypercholesterolaemia in high-risk patients or those with statin intolerance, but most probably also in improving long-term compliance of patients. These drugs, when affordable with a favourable cost-benefit profile, may also improve adherence [25].

Bempedoic acid is a prodrug that requires activation by the enzyme very-long-chain acyl-CoA synthetase 1, which is present in the liver but absent in muscle cells and which has been shown to be an interesting compound that acts upstream of HMG-CoA reductase. Bempedoic acid moderately lowers the LDL cholesterol level (~20%) and, interestingly, high-sensitivity C-reactive protein (CRP). Increase in gout attacks has been described [26]. If clinical outcome studies have favourable results, this drug may play a role either as combination therapy or in the case of statin intolerance.

As strongly emphasised in the ESC 2021 guidelines on cardiovascular prevention, a stepwise intensification of treatment for cardiovascular risk factors based on shared-decision making is recommended, taking into account residual cardiovascular risk factors (see below), as well as modifiers as poly-morbidity, poly-pharmacy, non-traditional psychological stress, frailty or unfavourable socioeconomic factors among others.

Residual risk and the need of a global risk assessment

Despite contemporary evidence based on therapeutic studies including best control of dyslipidaemia, a consistent residual risk of major cardiovascular events persists. Therefore, a global risk assessment including estimation of the residual risk should be considered in

all treated subjects (fig. 3). Residual triglyceride risk, residual lipoprotein a (Lp(a)) risk, residual inflammatory risk, residual thrombotic risk, and residual diabetes risk should be taken into account.

Residual triglyceride risk

The prevalence of elevated triglycerides in the general western population varies from 13.9% to 38.6%. The residual annual cardiovascular risk in high-risk patients on statins in contemporaneous trials varies from 1.5% to 4.5%. Residual risk seems to be elevated in subjects who also have hyperlipidaemia. According to the results of a meta-analysis of clinical and Mendelian randomised trials, triglyceride-rich lipoproteins probably do not induce atherosclerosis directly but through changes in LDL and high-density lipoprotein (HDL) metabolism [27]. This also probably explains why rem-

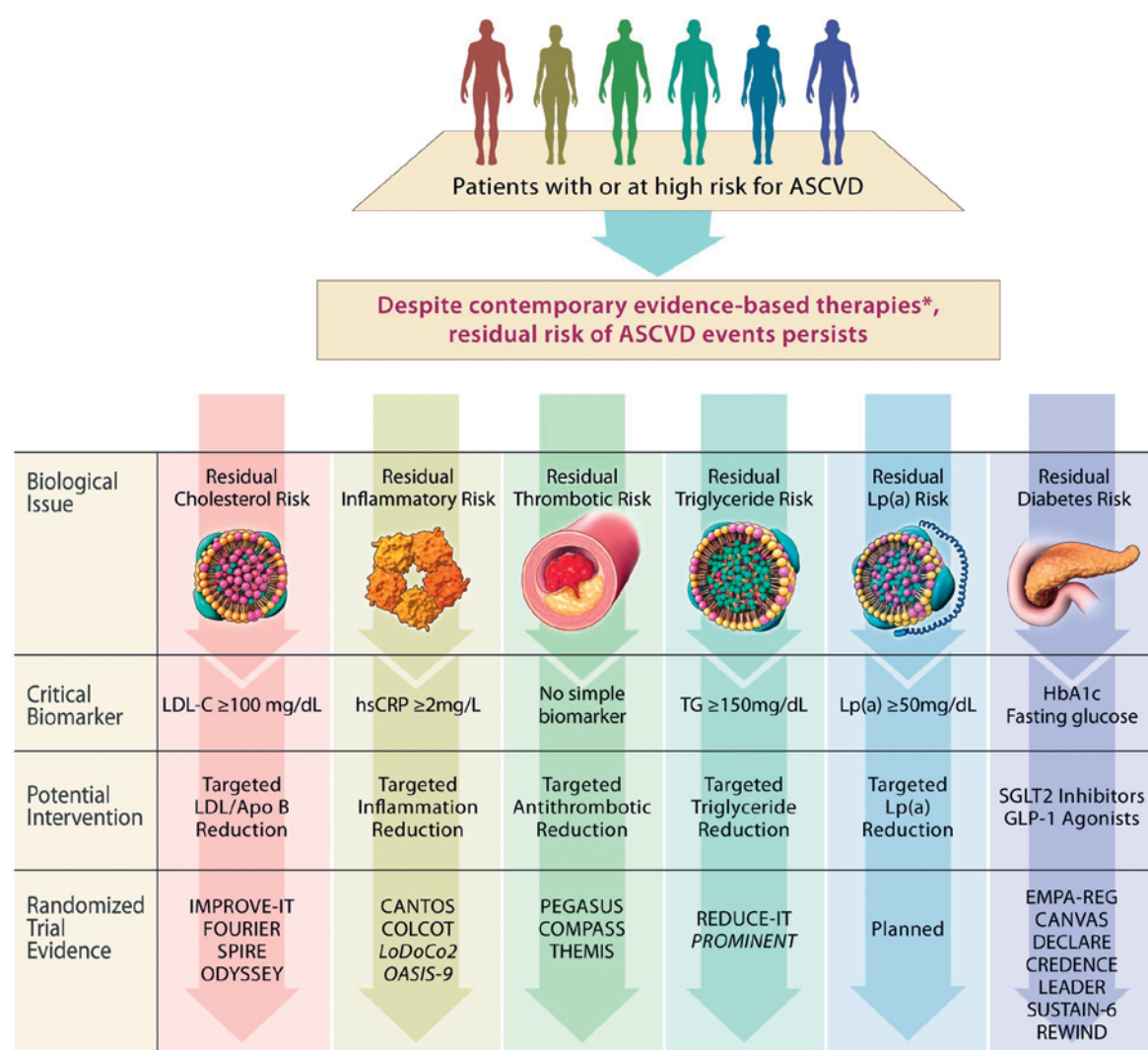


Figure 3: Residual risk and its components. Image reprinted with permission from Lawler PR, Deepak Bhatt DL, Godoy LC, Lüscher TF, Bonow RO, Verma S, Ridker PM Targeting cardiovascular inflammation: next steps in clinical translation Eur Heart J, 2021;42:113–131.

nant- and non-HDL cholesterol predict risk better than triglycerides. Although the specific mechanism of cardiovascular risk reduction by icosapent ethyl remains unknown (probably related to EPA-only omega-3 fatty acid), the REDUCE-it trial favours its use in severe hypertriglyceridaemia [28].

Residual lipoprotein a risk

Lp(a), a small LDL fragment bound to apoprotein B, can freely cross the endothelium into the vessel wall and, in analogy to the LDL molecule, increases the risk of ASCVD. Interestingly enough, its proatherogenic role is also related to a pro-coagulant effect due to its structural similarities to plasminogen; Lp(a) – through its oxidized phospholipid load – probably enhances an inflammatory response in the vessel wall [29]. Mendelian randomised trials have recently shown a straight forward correlation between Lp(a) serum level and the incidence of ASCVD [30].

There is evidence that PCSK9 inhibitors may significantly reduce the serum level of Lp(a), suggesting a potential role of these drugs in further reducing cardiovascular morbidity [31]. The ongoing Horizon trial will test whether a new promising antisense oligonucleotide will be capable of improving prognosis in patients with ASCVD and high Lp(a) levels. Among others under the perspective that in near future emerging treatment for this genetic determined metabolic disorder will be available, the ESC guidelines clearly advise measurement of serum Lp(a) once in life (indication level IIA, evidence level B).

Residual inflammatory risk

As mentioned above, inflammation is gathering an increasing role in atherosclerosis. The recent published CANTOS trial was the first prove of concept study of the inflammatory hypothesis in humans and seems to indicate that selected patients may probably profit from anti-inflammatory treatment in the future. Promising, although not conclusive results using old [32, 33], and emerging high selective drugs interfering with NLRP3 inflammasomes, will probably give us a definitive opportunity to tackle this residual risk [34].

Residual atherothrombotic risk

Atherothrombosis is crucial in the acute and chronic phases of the disease. Atherothrombosis is the final causal event leading to acute occlusion responsible of cardiovascular acute events: the underlying etiology of atherothrombosis include disruption of the atherosclerotic plaque and following thrombus formation. The major constituent of arterial thrombi are aggregated platelets following high viscosity. Fibrin formation

leading to thrombus elicited by the exposure of high thrombogenic material from the disrupted plaque (including overexpression of Tissue Factor – a trigger of the coagulation cascade) also play a major role in arterial thrombus initiation and propagation. Oxidative stress, hypoxia and inflammation are frequent conditions associated with atherothrombosis [35]. Atherothrombosis does not necessarily end-up in complete occlusion of the vessel and thus to an acute cardiovascular event. Healing of a ruptured atherosclerotic plaque occurs relatively frequently and constitutes an important process leading to progression or regression of atherosclerosis [36].

Residual diabetes and metabolic risk

We are all aware about the importance of the metabolic risk. For decades the obesity pandemic has been counteracting the overall trend toward reduction of ASCVD mostly by affecting young obese, and low-income population [37]. The metabolic risk is mainly but not exclusively driven by the presence of diabetes. There is large evidence that metabolic risk may be reduced by primordial prevention in obese children. The new ESC guidelines on dyslipidemia and on Diabetes and prediabetes and cardiovascular diseases clearly indicate that the management of diabetes mellitus – a multiplier of cardiovascular risk – is crucial in cardiovascular prevention. This has been even emphasized by the emerging role of new incoming potent antidiabetic drug families with a favorable trend in reducing ASCVD [37, 38].

Genetic risk and personalized medicine

Genetics is playing and will probably generate the unique chance to characterize patients and apparently healthy subjects at high residual risk; the paramount example is heterozygote familial hypercholesterolemia where genetic cascade testing allows to further increase our capability to detect patients at higher genetically determined risk. A running swiss prospective randomized AGLA-study entitled Cascade genetic Test in familial hypercholesterolemia (CATCH trial) supported by a competitive Swiss Heart Foundation grant will probably demonstrate feasibility and benefit of such detection strategy in our country. The rapid progress in the application of genomics will most probably change the approach of the management of several diseases including ASCVD. The expansion and increasing use of several -omics beyond genetics and the abovementioned huge capability of assembling big data will probably further influence our decision making within the framework of precision medicine.

Conclusion

Epidemiological, clinical and genetic studies have shown that the lower the LDL cholesterol level, the lower the risk of cardiovascular endpoints and that the earlier in life LDL cholesterol is lowered, the more effective the therapy. However, even if LDL-C is lowered a residual risk remains. This residual risk is composed of inflammatory risk, risk due to Lp(a) elevation, risk due to high triglycerides and increased risk due to glucose metabolism or coagulation or inflammatory problems. A comprehensive risk management therefore requires the correction of all risk factors, as envisaged in the concept of global risk management. In this context a major advance is represented by the innovative new risk calculator SCORE2 and SCORE2 OP derived and validated from the largest existing data-base representative of four large European areas with different cardiovascular risk prevalence. The new calculator defines both fatal and non-fatal ASCVD reflecting the whole spectrum of atherosclerotic burden, it also includes age-related risk stratification as well as lifelong risk estimation taking into account time-related exposure to the LDL burden; finally non-HDL-C serum level instead of LDL-C has been integrated in the new calculator as better representative of lipid risk factor. On the front of pharmacological drug prevention, major achievements have also been obtained during the last few years. Risk-adjusted statin either alone or combined with ezetimibe remains however the mainstay prevention drug regimen in dyslipidemia. The newcomer systemic delivered PCSK9 inhibitors either in form of monoclonal antibodies or silencing RNA have significantly broadened the spectrum of treatment. Their major hurdle remains the cost-benefit issue given the unaffordable high costs if all potentially qualified patients would be treated; this in spite of the recent price lowering of the PCSK9 antibodies. Further promising complementary drugs (bempedoic acid) and emerging new compounds will further enlarge the spectrum of antilipidemic strategy. Finally a stepwise treatment intensification of cardiovascular risk factors based on shared-decision making is always recommended.

Disclosure statement

No financial support and no other potential conflict of interest relevant to this article was reported.

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Key Points

- **A large body of evidence definitely demonstrates:**
 - the importance of the atherosclerotic burden of ASCVD
 - the paradigms “the lower is better”; and “the earlier and the longer is better”
- Cardiovascular prevention strategy should always initiate by risk estimation.
- patients and subjects at very high risk and high risk may be identified without need of risk calculators.
- **The new SCORE2 and SCORE2 OP risk calculator is a new extremely powerful algorithm based on one of the largest existing database:**
 - predicts 10-year risk of fatal and non fatal CV-events i.e. stroke and myocardial infarction
 - allows risk estimation and treatment according age (<50 y; 50–69 y; and >70 years)
 - non-HDL (total Cholesterol minus HDL - Cholesterol) is the reference lipid risk factor
 - lifelong risk estimation is an additional tool for refining risk assessment in young (and older)
 - AGLA advise to temporarily use both AGLA and SCORE2 / SCORE2 OP in order to get trained with and finally probably full adopt the new SCORE2 /SCORE 2OP
- **The concept of global risk management is stressed including:**
 - the importance of classical risks factors and modifiers (life-style, psychological stress, frailty, and unfavorable socioeconomic environment among others)
 - the concept of “residual risk” Lp(a), inflammatory-, atherothrombotic-, and metabolic risk. Lp(a) serum level should be measured once in life
- **Medical prevention of dyslipidemia follows the 2019 Guidelines on dyslipidemia enriched by the 2021 ESC guidelines on CV prevention:**
 - Very high risk and high risk patients or subjects should reach the serum LDL-C of <1.4 mmol/l and <1.8 mmol/L respectively
 - In case of recurrence of ACS the target serum LDL-C of <1.0 mmol could be considered
 - SCORE2 and SCORE2 OP generally allows a balanced age-related risk medical therapy: threshold level is lower in young persons and higher in older patients where
 - Secondary prevention is well established >70 years while evidence is less strong in primary prevention for very old, apparently healthy subjects
 - Lifelong risk estimation may be especially useful in primary prevention in young people
 - The 2021 ESC guidelines advise a stepwise treatment intensification based on shared-decision making
- **Anti-lipidemic drugs:**
 - High statins alone or in combination remain the main drug prevention treatment.
 - Ezetimibe in combination with high-dose statins achieves 65% reduction of LDL-C; it remains the drug of choice in case of statin intolerance even if patients should be encouraged to take the maximum tolerated dose of statin.
 - The newcomer bempedoic acid (20% LDL reduction) may also play a role either as combination therapy or in case of statin intolerance.
 - The new PCSK9 antibodies evolucumab and alirocumab, and the interfering RNA compound inclisiran constitute formidable weapons and are here to stay in secondary (and primary) prevention given their potency and the expected better long-term compliance. However, their broad utilization in clinical practice will depend on lowering of the actual still to high costs which yield a slow uptake of these drugs. For the time being their utilization is unfortunately limited to the very high risk or high patients.
 - Bempedoic acid may play a role either as combination therapy or in the case of statin intolerance
- **Areas of uncertainties:**
 - Several risk assessment and management contained in the more recent guidelines are still labelled with indication level IIB
 - Clinical outcome of incoming pharmacological therapies (inclisiran, bempedoic acid, antisense oligonucleotides) are not yet available although a benefit is most probably expected
 - icosapent ethyl is probably indicated in hypertriglyceridemia

References

The full list of references is included in the online version of the article at <https://cardiovascmed.ch/article/doi/CVM.2022.w10141>.