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Transatlantic Lipid Guideline Divergence: Same Data But Different Interpretations

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ABSTRACT: Despite consensus that excessive circulating concentrations of apoB-lipoproteins is a key driver for the atherosclerotic process and that treatments that low-density lipoprotein cholesterol lowering by up-regulation of low-density lipoprotein cholesterol receptor expression reduces that risk, divergent viewpoints on interpretation of study data have resulted in substantial differences in European and American lipid guideline recommendations. This article explores those differences and highlights the importance of understanding guideline-based lipid management to improve patient care and reduce the risk of clinical atherosclerotic cardiovascular disease.

Key Words: guideline ■ risk assessment ■ therapy

In response to the need for expert synthesis and guidance on the use of newer data on the management of lipid disorders for the prevention of clinical atherosclerotic cardiovascular disease (ASCVD), expert panels were convened in the United States and Europe, resulting in the publication of the 2018 American Heart Association/American College of Cardiology/Multi-Society (AHA/ACC/MS) Guideline on the Management of Blood Cholesterol[1] and the 2019 European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) Guidelines for the Management of Dyslipidemias: Lipid Modification to Reduce Cardiovascular Risk.[2] Both documents employ rankings of classes of recommendations and an assessment of supporting evidence, and advise preventive treatments in accordance with the estimated risk of the patient. These guidelines are based on data from Mendelian randomization, other genetic, epidemiological, and clinical studies that show, in agreement with a wealth of data derived from basic research, that excessive circulating concentrations of apoB (apolipoprotein B)-lipoproteins are a key driver of the atherosclerotic process[3] and that reduction of low-density-lipoprotein cholesterol (LDL-C) using interventions that decrease LDL-C by increasing LDL receptor expression reduce ASCVD risk, with the greatest benefit observed in those with a history of ASCVD, higher baseline LDL-C, diabetes mellitus, and other established risk factors. While there are many similarities between the 2 documents, there are also differences in interpretation of the evidence, resulting in different recommendations for lowering of LDL-C. This review highlights the similarities and differences between these documents and the divergent perspectives that result in these differences. It also provides illustrative case histories that highlight the clinical utility of both guidelines in the populations that they were designed to serve.

EXAMINING THE GUIDELINES: MAJOR SIMILARITIES BUT DIFFERENCES IN INTERPRETATION OF THE DATA

Both the 2018 AHA/ACC/MS Guideline and the 2019 ESC/EAS Guidelines employ a risk-based approach

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Nonstandard Abbreviations and Acronyms

AHA/ACC/MS	American Heart Association/ American College of Cardiology/ Multi-Society
ESC/EAS	European Society of Cardiology/ European Atherosclerosis Society
FH	familial hypercholesterolemia
PCSK9	proprotein convertase subtilisin/ kexin type 9
SCORE	Systematic Coronary Risk Evaluation

to grade intensity of the intervention and use patient history, clinical characteristics, and laboratory data to identify individuals most likely to benefit from lipid-lowering therapy. Both guidelines identify 4 major, mutually exclusive categories of patients likely to benefit from lipid-lowering interventions, including those with clinical ASCVD, severe primary hypercholesterolemia, diabetes mellitus, and primary prevention patients with high 10-year risk for ASCVD. They recommend treatments based on the premise that the higher the baseline risk, the greater the absolute ASCVD risk reduction derived from the same reduction of LDL-C. Some key differences in the interpretation of data include the following: definition of risk categories; employment of risk calculation systems that depend on ASCVD death (Systematic Coronary Risk Evaluation [SCORE]) versus fatal and nonfatal ASCVD (Pooled Cohort Equations); use of atherosclerosis imaging tests to inform treatment decisions; value of employing LDL-C goals, and, in selected hypertriglyceridemic patients, non–high-density lipoprotein cholesterol (non-HDL-C) and apoB goals, for clinical decision making; and use of pharmacotherapy that is based upon achieved LDL-C levels. While both guidelines recognize that there is a continuum of risk, the ESC/EAS Guidelines proceed on the premise that ASCVD risk is a continuum from low to very high without categorizing people to primary and secondary prevention, while the AHA/ACC/MS Guideline maintains that differentiation between primary and secondary prevention is warranted based on the results of randomized controlled trials. The 2019 ESC/EAS Guidelines provide a number of important updates to the previous ESC/EAS Guidelines of 2016 and among other key points, emphasize that lower LDL-C is better and that the absolute LDL-C reduction drives the clinical benefit (Data S1, Table S1). This perspective has led to new goals in high-risk and very high-risk patients, shifting the focus from high-intensity statin to high-intensity lipid-lowering. The philosophical underpinnings of these documents and their divergent approaches to lipid lowering for ASCVD risk reduction are summarized in Table 1.

WHAT ARE THE KEY DIFFERENCES BETWEEN THE ESC/EAS GUIDELINES AND THE AHA/ACC/MS GUIDELINE?

"Very High" Risk Categorization

Risk categorization of those at the highest end of the risk spectrum is quite divergent in the 2 guidelines (Table 2). The AHA/ACC/MS Guideline identifies "very high-risk" patients as those with recurrent major ASCVD events, or a major event plus >1 additional high-risk characteristic. Conversely, the ESC/EAS Guidelines characterize very high-risk individuals as those with clinical or unequivocal imaging evidence of ASCVD; diabetes mellitus with target organ damage, or with the presence of at least 3 major risk factors or type 1 diabetes mellitus of >20 years duration; chronic kidney disease with estimated glomerular filtration rate <30 mL/min per 1.73 m^2; or familial hypercholesterolemia (FH) with ASCVD or another risk factor. While there is no universally agreed-upon definition of "very high risk," and there is diversity in risk even among those classified as being at very high risk using the AHA/ACC/MS Guideline or the ESC/EAS Guidelines, both guidelines agree that these patients require aggressive preventive care. The differences in treatment recommendations relate to the almost exclusive dependence of the AHA/ACC/MS Guideline on randomized controlled trial data in specific patient populations to inform treatment recommendations, while the EAS/ESC Guidelines cast a broader net in very high-risk categorization, and treatment recommendations are based on the extrapolation of data showing that absolute risk reduction is greatest in those with the highest baseline risk.

Both guidelines favor the use of high-intensity, or maximally tolerated, statins as the first step in lipid-lowering pharmacotherapy (level IA in both). However, differences emerge in the recommendations for the use of nonstatins for patients with ASCVD. The AHA/ACC/MS Guideline suggests that ezetimibe therapy is reasonable (class IIa, B-R) in those at very high risk and with an LDL-C ≥1.8 mmol/L (70 mg/dL), and is recommended in those being considered for PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitor therapy (class I, B-NR). PCSK9 inhibitors are deemed reasonable only in very high-risk secondary prevention patients taking maximally tolerated statins and ezetimibe with LDL-C ≥1.8 mmol/L (70 mg/dL) or non-HDL-C ≥2.6 mmol/L (100 mg/dL) (class IIa, A). The ESC/EAS Guidelines provide a recommendation for the use of ezetimibe in those not achieving their LDL-C goals

Table 1. Comparison of the ESC/EAS Guidelines and the AHA/ACC/MS Guideline

Category	ESC/EAS Guidelines	AHA/ACC/MS Guideline
Overarching philosophy	The lower the achieved LDL-C, the better the outcomes	The best outcomes are achieved by adherence to RCT-proven therapies
Treatment decisions	Risk-based	Risk-based
Treatment objectives	Achieve LDL-C goals and, in patients with diabetes mellitus or the metabolic syndrome, non-HDL-C and apoB goals. Use statins first and add-on therapy as needed to achieve goals	Achieve desired percent LDL-C reduction. Use moderate- or high-intensity statins, and in selected individuals, add-on therapy for less-than-anticipated LDL-C reduction
Atherosclerosis imaging	Patients with imaging predictive of clinical events are considered very high risk and should be treated accordingly	Coronary calcium scoring is useful for discrimination, reclassification, and statin treatment allocation in borderline or intermediate-risk individuals
Lifestyle therapy	Is the basis for all lipid treatment therapy	Is the basis for all lipid treatment therapy
Statins	Maximally tolerated provides the greatest benefit	Maximally tolerated provides the greatest benefit
Ezetimibe	Use whenever LDL-C goals are not achieved on maximally tolerated statin therapy	Use in very high-risk or high-risk patients who achieve <50% LDL-C reduction with maximally tolerated statin therapy
PCSK9i	Use in very high-risk or selected high-risk patients whose LDL-C is not at goal on maximally tolerated statin therapy and ezetimibe	Consider use only in very high-risk ASCVD patients after maximally tolerated statin and ezetimibe if achieve <50% reduction in LDL-C and have LDL-C >1.8 mmol/L (70 mg/dL); or patients with baseline LDL-C ≥4.9 mmol/L (190 mg/dL) after maximally tolerated statin and ezetimibe if achieve <50% reduction in LDL-C and have LDL-C >2.6 mmol/L (100 mg/dL)
Categorization of very high-risk ASCVD	Clinical ASCVD; or ASCVD on imaging predictive of clinical events; or diabetes mellitus with target organ damage or ≥3 major risk factors; or severe CKD (<30 mL/min per 1.73 m^2); or SCORE risk ≥10%; or FH with ASCVD or another major risk factor	2 or more clinical ASCVD events or 1 major ASCVD event and 2 or more high-risk conditions
Diabetes mellitus	Risk stratify as moderate-, high, or very high risk depending on target organ damage, other major risk factors, and duration. LDL-C goal dependent on risk	Risk stratify as moderate- or high-risk. Moderate-intensity statin for most. High-intensity for those with additional major risk factors, especially in men >50 or women >60 y of age or with long-duration diabetes mellitus, end-organ disease, or ankle-brachial index <0.9
Severe primary hypercholesterolemia	High or very high risk. Use maximally tolerated statin, and if necessary, ezetimibe to lower LDL-C to <1.8 mmol/L (70 mg/dL). If additional risk factors consider very high-risk and treat to LDL-C <1.4 mmol/L (55 mg/dL). Consider PCSK9i if very high risk	High-risk. Use maximally tolerated statin to lower LDL-C to <2.6 mmol/L (100 mg/dL). If achieve <50% LDL-C reduction, add ezetimibe. May consider PCSK9i for HeFH patients with LDL-C ≥2.6 mmol/L (100 mg/dL) on maximally tolerated statin and ezetimibe
Primary prevention	Risk is assessment dependent on SCORE, employing fatal ASCVD events. Risk may be underestimated in those with risk-modifying factors. Atherosclerosis imaging may be employed in selected individuals to reclassify risk and alter treatment decisions. Treat to LDL-C goals	Risk assessment is dependent on the Pooled Cohort Equations, employing fatal and nonfatal myocardial infarction and stroke. Risk-enhancing factors in borderline or intermediate-risk patients may favor statin initiation or increased statin intensity. Coronary calcium scoring may be employed to aid in statin allocation in borderline or intermediate-risk individuals if statin treatment decision is uncertain
CKD	eGFR <30 mL/kg per 1.73 m^2 is a very high-risk condition. For stage 3–5 CKD patients not on hemodialysis, maximally tolerated statin and, if necessary, ezetimibe should be employed to reduce LDL-C to <1.4 mmol/L (55 mg/dL). No benefit to initiate statin therapy in patients on hemodialysis. Consider continuing statin and ezetimibe in patients on hemodialysis already taking these drugs	eGFR 15–59 mL/min per 1.73 m^2 is a risk-enhancing factor favoring initiation or intensification of statin therapy. No benefit to initiate statin therapy in patients on hemodialysis. Consider continuing statin and ezetimibe in hemodialysis patients already taking these drugs
Issues specific to women	No specific recommendations	Early menopause (<40 y of age) or preeclampsia are considered risk-enhancing factors
Older patients with ASCVD	Treat those >65 y of age the same as for younger patients	Treat those ≤75 y of age the same as younger patients. For those >75 y of age it is reasonable to initiate or continue moderate or high-intensity statin after consideration of adverse effects, drug–drug interactions, patient frailty, and patient preferences
Older patients without clinical ASCVD	Treat for primary prevention in those ≤75 y of age the same as younger individuals. Statin therapy may be considered in those >75 y of age, and if there is renal impairment or potential for drug interactions, start with low dose and titrate upward	May be reasonable to treat individuals >75 y of age with moderate-intensity statin; may consider statin discontinuation in those with physical or cognitive functional decline, multimorbidity, frailty, or reduced life expectancy, in whom these conditions limit potential for benefit. Coronary calcium scores of zero may be used; in those 76–80 y of age to avoid statin therapy

(*Continued*)

Table 1. (Continued)

Category	ESC/EAS Guidelines	AHA/ACC/MS Guideline
Heart failure with reduced ejection faction	Treatment with lipid-lowering therapy not recommended in the absence of other indications for its use	For those with ASCVD and not already on a statin, it may be reasonable to treat with moderate-intensity statin if life expectancy is at least 3 y

apoB indicates apolipoprotein B; AHA/ACC/MS, American Heart Association/American College of Cardiology/Multi-Society; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESC/EAS, European Society of Cardiology/European Atherosclerosis Society; FH, familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitors; RCT, randomized clinical trial; and SCORE, Systematic Coronary Risk Evaluation.

despite maximally tolerated statins (class I, B) and recommend PCSK9 inhibitors for very high-risk patients not achieving the LDL-C goals despite maximally tolerated statins and ezetimibe (class I, A). An additional recommendation of the ESC/EAS Guidelines and further departure from the AHA/ACC/MS Guideline for patients taking maximally tolerated statins and who experience a vascular event followed by a second vascular event within 2 years is that treatment to an LDL-C goal of <1 mmol/L (40 mg/dL) be considered (class IIb, C). Secondary treatment targets also include non-HDL-C and apoB, with goals being defined depending on the risk category: non-HDL-C <2.2 mmol/L (<85 mg/dL) and apoB <65 mg/dL for people at very high cardiovascular risk, and non-HDL-C <2.6 mmol/L (<100 mg/dL) and apoB <80 mg/dL for people at high cardiovascular risk, respectively.

Differences also emerge in the approach to treating older patients with ASCVD. The AHA/ACC/MS Guideline suggests that it is reasonable to treat patients with ASCVD >75 years of age with a moderate or high-intensity statin after evaluation of the potential for ASCVD risk reduction, adverse effects, drug–drug interactions, patient frailty, and preferences (class IIa, B-NR). The ESC/EAS Guidelines contend that treatment with statins should be the same in older (>age 65 years) patients with ASCVD as in younger patients (class I, A), with the provision that if there is significant renal impairment or the potential for drug–drug interactions, the statin should be started at a low dose and titrated upward to achieve LDL-C treatment goals (class I, C).

Diabetes Mellitus

Both sets of guidelines recognize that diabetes mellitus is an intermediate- to high-risk condition in which additional information may help to more reliably quantify risk. The AHA/ACC/MS Guideline recommends the use of at least moderate-intensity statins for all patients with diabetes mellitus (class I, A), but those with multiple risk factors may reasonably be treated with a high-intensity statin (class IIa, B-NR). If the clinician chooses to use the Pooled Cohort Equations for further risk stratification, patients with a ≥20% 10-year risk may be considered for high-intensity statins, or, if needed, ezetimibe to lower LDL-C by ≥50% (class IIb, C-LD). A weak recommendation is given for the initiation of statins in patients who have diabetes mellitus and

Table 2. Very High-Risk Categorization

AHA/ACC/MS Guideline	ESC/EAS Guidelines
Two or more major ASCVD events: • Recent ACS (within the past 12 mo) • History of MI (other than the recent ACS event listed above) • History of ischemic stroke • Symptomatic peripheral arterial disease (history of claudication with ABI <0.85, or previous revascularization or amputation) Or One major event and >1 high-risk condition • Age ≥65 y • Heterozygous FH • History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s) • Diabetes mellitus • Hypertension • CKD (eGFR 15–59 mL/min per 1.73 m^2) • Current smoking • Persistently elevated LDL-C ≥100 mg/dL (2.6 mmol/L) despite maximally tolerated statin therapy and ezetimibe History of congestive heart failure	Any one of those below: • Documented clinical ASCVD • Unequivocal ASCVD on imaging predictive of ASCVD events • Type 2 diabetes mellitus with target organ damage (microalbuminuria, retinopathy, or neuropathy), or at least 3 major risk factors, or early-onset T1DM of long duration (>20 y) • Severe CKD (eGFR <30 mL/min per 1.73 m^2). • A calculated SCORE ≥10% or 10-y risk of fatal CVD • FH with ASCVD or with another major risk factor

ABI indicates ankle-brachial index; ACS, acute coronary syndrome; AHA/ACC/MS, American Heart Association/American College of Cardiology/Multi-Society; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ESC/EAS, European Society of Cardiology/European Atherosclerosis Society; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; SCORE, Systematic Coronary Risk Estimation; and T1DM, type 1 diabetes mellitus.

who are > 75 years of age (class IIb, C-LD). Younger patients 20 to 39 years of age who have had type 2 diabetes mellitus for ≥10 years, or >20 years of type 1 diabetes mellitus, and have evidence of end-organ involvement or an ankle–brachial index <0.9 also have a weak recommendation for initiation of statin therapy (class IIb-C-LD).

These recommendations stand in contrast to those of the ESC/EAS Guidelines, which stratify patients with diabetes mellitus as a moderate-, high-, or very high-risk, depending on the duration of diabetes mellitus, number of concomitant risk factors, end-organ damage, and age of the patient. Those with target organ damage, at least 3 risk factors, or type 1 diabetes mellitus of >20 years duration are classified as very high risk for which an LDL-C goal of <1.4 mmol/L (55 mg/dL) is recommended (class I, A). Diabetes mellitus without target organ damage, duration <10 years, and no additional risk factors is considered a high-risk state, for which an LDL-C goal of <1.8 mmol/L (70 mg/dL) is recommended (class I, A). Moderate-risk diabetes mellitus is considered to be present in those who have type 1 diabetes mellitus and who are <35 years of age or with type 2 diabetes mellitus <50 years of age with duration of diabetes <10 years with no evidence of target organ involvement. The LDL-C goal in such patients is <2.6 mmol/L (100 mg/dL) (class IIa, A). Finally, statin therapy may be considered in patients who have both type 1 and type 2 diabetes mellitus and who are ≤30 years of age with evidence of end organ damage and/or an LDL-C level >2.5 mmol/L, so long as pregnancy is not being planned (class IIb, C). However, because of the nature of diabetic dyslipidemia, LDL-C level measurements may not be an effective tool to unveil lipid abnormalities, which instead may be better reflected by non-HDL-C and apoB levels. This is the reason for introducing these secondary goals in the guidelines because they capture the elevated burden of non-LDL atherogenic lipoproteins.

Severe Primary Hypercholesterolemia including FH

Another difference between the 2 Guidelines relates to the intensity of treatment and LDL-C goals in patients with severe hypercholesterolemia. The AHA/ACC/MS Guideline recognizes the high risk associated with LDL-C ≥4.9 mmol/L (190 mg/dL), but provides slightly different recommendations for those who meet the diagnostic criteria for FH as compared with those who do not. In both cases, the use of maximally tolerated statin is recommended. For those 20 to 75 years of age unable to achieve a ≥50% LDL-C reduction and/or have an LDL-C ≥2.6 mmol/L (100 mg/dL), the addition of ezetimibe therapy is classified as reasonable (class IIa, B-R). The addition of a bile acid sequestrant for those achieving <50% reduction from baseline LDL-C and having fasting triglycerides <3.4 nmol/L (300 mg/dL) may be considered (class IIb, B-R). For those 40 to 75 years of age with baseline LDL-C ≥5.7 mmol/L (220 mg/dL) taking maximally tolerated statins and ezetimibe and with a persistent LDL-C ≥3.4 mmol/L (130 mg/dL), the addition of a PCSK9 inhibitor may be reasonable (class IIb, C-LD). For those patients 30 to 75 years of age with heterozygous FH with an LDL-C ≥2.6 mmol/L while taking maximally tolerated statin and ezetimibe, the addition of a PCSK9 inhibitor may be considered (class IIb, B-R).

The ESC/EAS Guidelines identify anyone with a total cholesterol >8 mmol/L (310 mg/dL) or LDL-C >4.9 mmol/L (190 mg/dL) as high-risk and maximally tolerated statin plus, if needed, ezetimibe should be used to achieve an LDL-C goal <1.8 mmol/L (70 mg/dL). Those with FH and concomitant ASCVD or another risk factor are considered very high risk. Treatment with a maximally tolerated statin and, if needed, ezetimibe is recommended (class I, C). A PCSK9 inhibitor should be added if LDL-C remains ≥1.4 mmol/L (55 mg/dL) for those at very high risk (class I, C) and is reasonable for those at high risk with LDL-C above goal (class IIa, C). The Guidelines identify very high-risk primary prevention patients as those with FH without ASCVD or additional risk factors and suggest that treatment to an LDL-C goal of <1.4 mmol/L (55 mg/dL) is reasonable (class IIa, C). The addition of a bile acid sequestrant may be considered for those who do not achieve their LDL-C goals despite maximal statin therapy (class IIb, C).

Primary Prevention

According to the AHA/ACC/MS Guideline, primary prevention patients are classified into various categories of 10-year risk for fatal or nonfatal ASCVD using the Pooled Cohort Equations. Low risk is defined as <5%, borderline 5% to 7.4%, intermediate 7.5% to 19.9%, and high ≥20%. Younger patients, particularly those <40 years of age, are counseled on preventive therapy using lifetime ASCVD risk estimates, also provided as part of the Pooled Cohort Equation risk calculator. Lifestyle therapy alone is recommended for most patients at low risk, consideration of moderate-intensity statin for those at borderline risk if risk-enhancing factors (Table 3) are present (class IIb, B-R), use of moderate-intensity statins for those at intermediate risk (class I, A) and a high-intensity statin for those at high risk, with an objective to lower LDL-C by ≥50% (class I, A).

Treatment decisionmaking in the borderline or intermediate-risk groups is more nuanced and may be influenced by the presence of risk-enhancing factors.

Table 3. Factors Modifying Risk Assessment in Primary Prevention

AHA/ACC/MS Guideline	ESC/EAS Guidelines
Risk-enhancing factors	Risk-modifying factors

• Family history of premature ASCVD (men, age <55 y; women, age <65 y)
• Primary hypercholesterolemia, LDL-C 4.1–4.9 mmol/L (160–189 mg/dL) or non–HDL-C 4.9–5.7 mmol/L (190–219 mg/dL)
• Metabolic syndrome (increased waist circumference, elevated triglycerides (>1.7 mmol/L [150 mg/dL]), elevated blood pressure, elevated glucose, and low HDL-C (<1.0 mmol/L [40 mg/dL]) in men; (<1.3 mmol/L [50 mg/dL]) in women
• CKD (eGFR 15–59 mL/min per 1.73 m^2 with or without albuminuria, and not dialysis or kidney transplantation)
• Chronic inflammatory conditions (eg, psoriasis, rheumatoid arthritis, HIV/AIDS)
• History of premature menopause (before age 40 y) and history of pregnancy-associated conditions that increase later ASCVD risk (eg, preeclampsia)
• High-risk race/ethnicities (eg, South Asian ancestry)
• Lipid biomarkers associated with increased ASCVD risk:
  ○ Persistently elevated primary hypertriglyceridemia (≥175 mg/dL) optimally on 3 determinations
  ○ If measured:
  ▪ High-sensitivity C-reactive protein ≥2.0 mg/L
  ▪ Elevated lipoprotein(a) ≥50 mg/dL (≥125 nmol/L)
  ▪ Elevated apolipoprotein B ≥130 mg/dL
  ▪ Ankle–brachial index <0.9
	• Social deprivation: the origin of many of the causes of CVD
	• Obesity and central obesity as measured by the body mass
	• Index and waist circumference, respectively
	• Physical inactivity
	• Psychosocial stress including vital exhaustion
	• Family history of premature CVD (men: <55 y and women: <60 y)
	• Chronic immune-mediated inflammatory disorder
	• Treatment for HIV infection
	• Atrial fibrillation
	• Left ventricular hypertrophy
	• CKD
	• Obstructive sleep apnea syndrome
	• Nonalcoholic fatty liver disease

AHA/ACC/MS indicates American Heart Association/American College of Cardiology/Multi-Society; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ESC/EAS, European Society of Cardiology/European Atherosclerosis Society; HDL-C, high-density lipoprotein cholesterol; and LDL-C, low-density lipoprotein cholesterol.

If the decision about treatment is still uncertain, coronary calcium scoring may be considered (class IIa, B-NR). The absence of coronary calcium favors lifestyle therapy alone except in those who have diabetes mellitus, are active cigarette smokers, or have a strong family history of premature ASCVD (class IIa, B-NR) for whom statin therapy may still be considered. A calcium score of ≥100 Agatston units favors the initiation of statin therapy (class IIa, B-NR). Those patients with calcium score of 1 to 99 Agatson units are advised to have a clinician–patient discussion, although statin therapy is favored in such patients who are ≥55 years of age (class IIa, B-NR).

Like the AHA/ACC/MS Guideline, the ESC/EAS Guidelines identify primary prevention patients with low, moderate, and highrisk using the SCORE risk calculator. However, they also define a very high-risk primary prevention group. The use of SCORE means that fewer primary prevention patients are recommended treatment versus the Pooled Cohort Equations or other risk scoring systems using fatal and nonfatal events. This is relevant to the preventive care of younger patients in whom the relative risk charts can be used as a means to improve discussions between patients and physicians.

Low-risk patients using SCORE have a 10-year calculated risk of fatal cardiovascular disease of <1%. Those with a calculated risk of ≥1 to <5% are at moderate risk; ≥5 to <10% are at highrisk, and those with ≥10% are at very high risk. The presence of any of a number of risk-modifying factors (Table 3) may be used to up-classify SCORE calculated risk. The LDL-C treatment goals for low-, moderate-, high-, and very high-risk patients are <3.0 mmol/L (116 mg/dL), <2.6 mmol/L (100 mg/dL), <1.8 mmol/L (70 mg/dL), and <1.4 mmol/L (55 mg/dL), respectively. The ESC/EAS Guidelines also identify secondary goals for non-HDL-C of <3.4, <2.6, and <2.2 mmol/L (<100, <80, and <65 mg/dL, respectively) for moderate-, high-, and very high-risk patients, and apoB secondary goals of <100, <80, and <65 mg/dL, respectively. Pharmacotherapy includes statin therapy first, ezetimibe second, and PCSK9 inhibitors third, if needed to achieve the above goals, with the option of adding a bile acid sequestrant if deemed clinically appropriate.

Chronic Kidney Disease

The AHA/ACC/MS Guideline identifies chronic kidney disease (estimated glomerular filtration rate 15–59 mL/min per 1.73 m^2) as a risk-enhancing factor that favors statin initiation in patients not treated with dialysis or renal transplantation at intermediate 10-year ASCVD risk using the Pooled Cohort Equations (class IIa, B-R). Those patients receiving hemodialysis who are already taking a statin may reasonably be continued on their statin (class IIb, C-LD). Statin initiation is not recommended in those hemodialysis patients who are not currently taking statins (level III, no benefit).

The ESC/EAS Guidelines use severe chronic kidney disease (estimated glomerular filtration rate <30 mL/min per 1.73 m^2) to define very high-risk patients, and moderate chronic kidney disease (estimated glomerular filtration rate 30–59 mL/min per 1.73 m^2) to classify patients as high risk. Statins

or statin/ezetimibe combination therapy is recommended in patients with stage 3 to 5 non–dialysis-dependent chronic kidney disease (class I, A). PCSK9 inhibitor therapy is not addressed in these patients. Continuation of statins or statin/ezetimibe combination therapy in those taking these drugs at the time of dialysis is reasonable, especially if they have ASCVD (class IIa, C). The initiation of statins in hemodialysis patients not taking these drugs is not recommended (class III, A).

Issues Specific to Women

The AHA/ACC/MS Guideline identifies a history of premature menopause (before 40 years of age) or a history of pregnancy-associated conditions that increase later ASCVD risk, such as preeclampsia, as a risk-enhancing factor favoring statin initiation in borderline or intermediate-risk patients. The ESC/EAS Guidelines do not differentiate between the sexes for statin treatment guidelines in primary or secondary prevention and do not mention the above factors as indictors of increased ASCVD risk.

Hypertriglyceridemia

While the AHA/ACC/MS Guideline is identified as a guideline on the management of blood cholesterol, it also provides recommendations on the management of triglyceride disorders. It defines hypertriglyceridemia as a fasting level ≥2 mmol/L (175 mg/dL), which, if persistent on 3 determinations, is a risk-enhancing factor favoring statin initiation in primary prevention patients 40 to 75 years of age with a 5% to 19.9% 10-year ASCVD risk using the Pooled Cohort Equations. In patients with hypertriglyceridemia, the AHA/ACC/MS Guideline also suggests that apoB measurements may have advantages, especially in individuals with triglycerides ≥2.3 mmol/L (200 mg/dL). An apoB level ≥130 mg/dL constitutes a risk-enhancing factor favoring initiation of a moderate-intensity statin, or intensification of statin therapy in those already taking a moderate-intensity statin (class IIa, B-R). In those with severe hypertriglyceridemia of ≥5.7 mmol/L (500 mg/dL) and a 10-year risk ≥7.5%, it is reasonable, after addressing possible secondary causes, to initiate a moderate- or high-intensity statin (level IIa, B-R). Further intensification of diet therapy and treatment with omega-3 fatty acids or, if needed, fibrates should be considered in those with triglycerides ≥11.3 mmol/L (1000 mg/dL) to reduce the likelihood of acute pancreatitis (class IIa, B-NR).

The ESC/EAS Guidelines identify a level of fasting triglycerides of ≥1.7 mmol/L (150 mg/dL) as being associated with increased ASCVD risk. While exclusion of secondary causes and dietary measures are advised in all such patients, statins are recommended as the initial drug of choice in high-risk individuals with triglycerides >2.3 mmol/L (200 mg/dL) (class I, B). Fibrates may be considered for high-risk, statin-treated patients whose triglycerides remain above this level (class IIb, B) and for statin-treated primary prevention patients with similar degrees of hypertriglyceridemia (class IIb, B). Based on the results of a randomized controlled trial not available at the time of the evidence review for the AHA/ACC/MS Guideline,[4] the ESC/EAS Guidelines indicated that the addition of icosapent ethyl 2 g twice daily is reasonable for high-risk patients with triglyceride levels between 1.5 and –5.6 mmol/L (135–499 mg/dL) despite statin treatment (IIa, B). In addition to triglyceride levels, icosapent ethyl has been shown to reduce non-HDL-C and apoB levels, thus reducing atherogenic particle concentrations.

The ESC/EAS Guidelines recognize that the risk for acute pancreatitis is significantly increased in those with triglycerides >10 mmol/L (880 mg/dL), and, like the AHA/ACC/MS Guideline, recommends that dietary factors, including alcohol, should be addressed, and that a very-low-fat diet (10%–15% of total calories) should be initiated. Addressing glycemic control for those with diabetes mellitus and the initiation of fenofibrate and adjunctive therapy with 2 to 4 g daily of omega-3 fatty acids are advised.

Illustrative Cases Demonstrating Divergence of Guideline-Based Treatment

The contrasting approaches to patient management using the ESC/EAS Guidelines versus the AHA/ACC/MS Guideline are illustrated in the cases presented in Table 4. The different recommendations for guideline-based patient care, despite the availability to the guideline writers of a similar body of literature, reinforce the perspective that there are multiple approaches to evidence-based lipid management for ASCVD risk reduction.

CONCLUSIONS

The ESC/EAS Guidelines and the AHA/ACC/MS Guideline represent the synthesis by panels of experts of the best available data to inform risk assessment and treatment decisions about lipid management for the prevention of ASCVD. While both guidelines recognize the value of LDL-C lowering as a key strategy to prevent clinical events, divergent interpretation and application of the evidence results in some differences in treatment recommendations. The most striking difference is that the ESC/EAS Guidelines embrace the concept of LDL-C goals, affirm that defined goals are of value both to the patient and

Table 4. Illustrative Cases

Case 1. A 50-y-old man of Lebanese ethnicity has an 8-y history of type 2 diabetes mellitus and is taking antihypertensive therapy. He does not have clinical ASCVD, does not have known complications from diabetes mellitus, and has no additional major cardiovascular risk factors. He does not take lipid-lowering medication. His blood pressure is 128/78 mm Hg. His fasting lipid panel shows total cholesterol 5.4 mmol/L (209 mg/dL), HDL-C 1.2 mmol/L (46 mg/dL), triglycerides 1.4 mmol/L (120 mg/dL), and LDL-C 3.6 mmol/L (139 mg/dL). He has an eGFR of 55 mL/min per 1.73 m^2

Guideline	Risk Level	Rationale	Treatment Objective	Statin Therapy	Add-on Therapy
ESC/EAS	High	Diabetes mellitus with 1 additional risk factor	LDL-C reduction ≥50%, <1.8 mmol/L (70 mg/dL)	Maximally tolerated (class I, A)	Ezetimibe because LDL-C above goal (class I, B)
AHA/ACC/MS	Intermediate	Diabetic with <2 other risk factors	LDL-C reduction 30–49%	Moderate intensity (class I, A)	No add-on therapy indicated
Key point: Higher risk categorization for patients with diabetes mellitus with 1 additional risk factor is recommended in the ESC/EAS Guidelines compared with the AHA/ACC/MS Guideline					

Case 2. A 62-y-old Hispanic woman had an acute myocardial infarction 3 y ago and was treated with percutaneous intervention. She smoked 1 pack of cigarettes per day for 25 y, but stopped smoking at the time of her myocardial infarction. She has no other major ASCVD risk factors. Her baseline lipid panel showed total cholesterol 6.7 mmol/L (260 mg/dL), HDL-C 1.2 mmol/L (48 mg/dL), triglycerides 1.8 mmol/L (160 mg/dL), and LDL-C 4.7 mmol/L (180 mg/dL). Following treatment with atorvastatin 80 mg daily, her LDL-C was 3.1 mmol/L (120 mg/dL). She was then treated with ezetimibe, with a resultant LDL-C of 2.6 mmol/L (102 mg/dL)

Guideline	Risk Level	Rationale	Treatment Objective	Statin Therapy	Add-on Therapy
ESC/EAS	Very high	ASCVD with LDL-C above goal	LDL-C reduction ≥50%, <1.4 mmol/L (55 mg/dL)	Maximally tolerated (class I, A)	PCSK9i because LDL-C above goal (class I, A)
AHA/ACC/MS	High	Uncomplicated ASCVD	LDL-C reduction ≥50%	Maximally tolerated (class I, A)	Ezetimibe because LDL-C above treatment threshold >1.8 (70 mg/dL) Class IIb, B-R
Key point: Very high-risk categorization for patients with ASCVD is broader in the ESC/EAS Guidelines than in the AHA/ACC/MS Guideline					

Case 3. A 60-y-old Hungarian man has a history of hypertension, obesity, paroxysmal atrial fibrillation, and left ventricular hypertrophy. He is a nonsmoker, does not have diabetes mellitus, and has no family history of premature ASCVD. His waist circumference is 127 cm (50 in). His blood pressure on antihypertensive drug therapy is 140/80 mm Hg. His 10-y risk using SCORE was 5%, and using the Pooled Cohort Equations (PCE) was 15%. His lipid panel shows a total cholesterol 5.9 mmol/L (228 mg/dL), HDL-C 1.1 mmol/L (42 mg/dL), triglycerides 1.7 mmol/L (155 mg/dL), and LDL-C 4.0 mmol/L (155 mg/dL). He has an eGFR >90 mL/min per 1.73 m^2

Guideline	Risk Level	Rationale	Treatment Objective	Statin Therapy	Add-on Therapy
ESC/EAS	High	SCORE risk 5%, LVH and atrial fibrillation	LDL-C reduction ≥50%, <1.8 mmol/L (70 mg/dL); non-HDL-C <2.6 mmol/L (100 mg/dL), apoB <80 mg/dL	Maximally tolerated (class I, A)	Ezetimibe if needed to achieve LDL-C goal (class I, B)
AHA/ACC/MS	Moderate	PCE risk 15%, metabolic syndrome	30–49% LDL-C reduction	Moderate intensity (class I, A)	No add on therapy indicated
Key point: High-risk categorization for primary prevention using SCORE in setting of risk-modifying factors categorizes this patient as high risk, as compared with moderate risk using the Pooled Cohort Equations in the AHA/ACC/MS Guideline.					

Case 4. A 50-y-old Israeli man has a 15-y history of type 2 diabetes mellitus and has proliferative retinopathy, hypertension, and chronic kidney disease. He smokes 20 cigarettes per day. His blood pressure is 125/75 mm Hg on antihypertensive drug therapy. He has a waist circumference 112 cm (44 in). His baseline lipid panel showed a total cholesterol of 6.7 mmol/L (258 mg/dL), HDL-C 0.7 mmol/L (25 mg/dL), triglycerides 2.9 mmol/L (260 mg/dL), and LDL-C 4.7 mmol/L (181 mg/dL). He was initially treated with atorvastatin 80 mg daily and when he had a persistently elevated LDL-C level, ezetimibe was added. His current lipid panel shows a total cholesterol of 4.3 mmol/L (166 mg/dL), HDL-C 0.8 mmol/L (30 mg/dL), triglycerides 2.6 mmol/L (230 mg/dL), and LDL-C 2.3 mmol/L (90 mg/dL). He has an eGFR of 48 mL/min per 1.73 m^2, and a urine albumin/creatinine ratio of 100 mg/g creatinine

Guideline	Risk Level	Rationale	Treatment Objective	Statin Therapy	Add-on Therapy
ESC/EAS	Very high	Diabetes mellitus with target organ damage	LDL-C reduction ≥50%, <1.4 mmol/L (55 mg/dL); non-HDL-C <2.2 mmol/L, apoB <65 mmol/L	Maximally tolerated (class I, A)	PCSK9i (class IIb, C) or BAS (class IIb, C) to achieve LDL-C goal. IPE reasonable (class IIa, B). Fibrate may be reasonable (class IIb, C).
AHA/ACC/MS	High	Diabetes mellitus, 3 additional risk factors and DM risk enhancers	LDL-C reduction ≥50%	Maximally tolerated (class I, A)	No additional add-on therapy indicated
Key point: Very high-risk categorization for patients with diabetes mellitus with target organ damage using the ESC/EAS Guidelines results in higher risk status than AHA/ACC/MS Guideline					

(*Continued*)

Table 4. Continued

Case 5. A 45-y-old White woman is referred to the Lipid Clinic because of severe hypercholesterolemia and a family history of hypercholesterolemia (FH) and premature coronary artery disease. She is asymptomatic, has no other ASCVD risk factors, and has normal physical examination results, with no corneal arcus or tendon xanthomas. Her initial lipid profile showed total cholesterol of 7.8 mmol/L (300 mg/dL), HDL-C 1.6 mmol/L (60 mg/dL), triglycerides 1.1 mmol/L (100 mg/dL), and LDL-C 5.7 mmol/L (220 mg/dL). She was confirmed by genetic testing to harbor an LDL receptor genetic variant consistent with heterozygous FH. She was treated with lifestyle counseling, a high-intensity statin and ezetimibe, and her on-treatment LDL-C is now 2.3 mmol/L (90 mg/dL)					
Guideline	**Risk Level**	**Rationale**	**Treatment Objective**	**Statin Therapy**	**Add-on Therapy**
ESC/EAS	High	FH without other major risk factors	LDL-C reduction ≥50%, <1.8 mmol/L (70 mg/dL)	Maximally tolerated (class I, A)	BAS if above goal (class IIb, C)
AHA/ACC/MS	High	FH without other major risk factors	LDL-C reduction ≥50%, LDL-C <2.6 mmol/L (100 mg/dL)	Maximally tolerated (class I, A)	None
Key point: While both Guidelines categorize this patient at high risk, the ESC/EAS Guidelines advocate a lower LDL-C goal for patients with FH without additional risk factors than the AHA/ACC/MS Guideline.					
Case 6. A 60-y-old woman of Italian ethnicity comes to the Lipid Clinic because of multiple LDL-C measurements between 4.2 mmol/L (162 mg/dL) and 4.8 mmol/L (186 mg/dL) and most recently, 4.7 mmol/L (180 mg/dL). Her blood pressure was 140/78 mm Hg. She had complained of intolerable myalgias while taking 4 different statins, 2 of which were at their starting doses. Her thyroid-stimulating hormone, free thyroxine, 25-hydroxyvitamin D, and creatine kinase levels were normal. Her father had a myocardial infarction at 61 y of age. The patient is worried about her cardiovascular risk, but is hesitant to take another statin. Her SCORE 10-y risk is 1%. Her Pooled Cohort Equations 10-y risk is 5.1%. A coronary artery calcium scoring test was performed and she was found to have a score of zero					
Guideline	**Risk Level**	**Rationale**	**Treatment Objective**	**Statin Therapy**	**Add-on Therapy**
ESC/EAS	Moderate	SCORE risk 1%	LDL-C <2.6 mmol/L (100 mg/dL)	Consider less than daily statin to achieve LDL-C goal	Consider ezetimibe if LDL-C persistently ≥3.0 mmol/L (class I, B)
AHA/ACC/MS	Low	Calcium score zero "de-risks" her from borderline to low	Lifestyle therapy	None (class IIa, B-NR)	None
Key point: The ESC/EAS Guidelines advise consideration of drug therapy in addition to lifestyle therapy for those with SCORE calculated risk ≥1%. The AHA/ACC/MS Guideline advises deferral of drug therapy for borderline-risk individuals with a coronary calcium score of zero, in the absence of cigarette smoking, diabetes mellitus, or a strong family history of premature ASCVD.					

AHA/ACC/MS indicates American Heart Association/American College of Cardiology/Multi-Society; apoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; BAS, bile acid sequestrant; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; ESC/EAS, European Society of Cardiology/European Atherosclerosis Society; FH, familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; IPE, icosapent ethyl; LDL-C, low-density lipoprotein cholesterol; LVH, left ventricular hypertrophy; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; and SCORE, Systematic Coronary Risk Evaluation.

clinician, and target treatment to those goals. The specific goals are lower than those dictated by the AHA/ACC/MS concept of treatment thresholds, levels above which nonstatins may be considered for addition to maximally tolerated statins. The ESC/EAS Guidelines are less strictly adherent than the AHA/ACC/MS Guideline to the patient groups shown to derive ASCVD risk reduction based on randomized controlled trials. Even with the most aggressive LDL-C-lowering treatments, residual risk for ASCVD events is still present, and the consistency of benefit seen with more aggressive LDL-C lowering and the safety of drugs that act via the mechanism of increased expression of LDL receptors serve as a reasonable rationale for this approach.

Despite these differences, both guidelines affirm the central role of shared decisionmaking in all clinician–patient interactions, because no treatment recommendation provides benefit unless it is accepted and integrated into his or her life by the patient. There is evidence that those individuals who engage in shared decision making have better health outcomes, more positive healthcare experiences, and lower healthcare expenditures.[5,6] Such interactions are of particularly great importance when decisions to employ imaging tests that may increase patient expenditures, or costly medications, such as PCSK9 inhibitors, are being made. In the case of PCSK9 inhibitors, both guidelines agree that because of the high cost of these medications, their use should be reserved only for those deemed to be at very high risk for ASCVD events.

Despite the publication of these 2 well-respected and clinically relevant guideline documents, there still remains a large gap in guideline implementation and adherence to recommended treatments. Patient reminders, simplification of drug treatment regimens, clinician education, and expanded utilization of nonphysician members of the healthcare team are clearly needed in both Europe and the United States to promote guideline-based medical therapy. Continued academic engagement of colleagues on both sides of the Atlantic will continue to promote high-quality lipid management for the prevention of ASCVD.

ARTICLE INFORMATION

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Supplemental Material

Data S1
Table S1
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Supplemental Material

Data S1.

What's New in the ESC/EAS Guidelines

Reclassification of ASCVD risk for selected patients with familial hypercholesterolemia and new LDL-C treatment goals

Based on the genetic evidence and the results of randomized clinical controlled trials with PCSK9 inhibitors, which showed that extreme reductions of LDL-C can be achieved safely and translate into a reduction of CV events [7-11], the new guidelines have significantly lowered LDL-C goals for each risk except the low risk category. Similar levels of relative ASCVD risk reduction per mmol LDL-C reduction are seen with the use of all type of interventions. A meta-analysis of 49 studies comparing the effects of different types of lipid-lowering therapies showed that all these approaches reduced the relative hazard for CV events by 20-25% per mmol/L of LDL-C reduction [12]. This observation is in line with data from Mendelian randomization studies, which show that genetic variants associated with lower LDL-C levels have similar effects on the risk of CHD per unit lower LDL-C, although the degree of risk reduction is larger than observed in RCTs of LDL-C lowering interventions, which may reflect the effect of differences in the cumulative exposure to the risk factor over time[13]. ASCVD risk categorization in the new Guidelines is similar to the 2016 ECS/EAS Guidelines, but with several modifications.

A new feature is that FH with ASCVD or an additional risk factor is now considered a very-high-risk state and FH in their absence is deemed a high-risk state. The LDL-C goals for very-high, high-, and moderate-risk patients are now <1.4 mmol/L (55 mg/dL), <1.8 mmol/L (70 mg/dL), and <2.6 mmol/L (100 mg/dL), respectively. Patients with advanced CKD (<30 mL/min/1.73 m^2) continue to be categorized as very-high-risk, although treatment recommendations differ depending upon whether the patients are managed with or without hemodialysis. In the latter group, LDL-lowering therapy is not associated with significant ASCVD risk reduction, likely due to competing co-morbidities. Whereas the previous Guidelines recommended a single goal for moderate- or low-risk patients, the current guidelines advise an LDL-C goal of <3.0 mol/L

(116 mg/dL) only for low risk patients. Further for patients with a recurrent ASCVD event within two years an LDL goal of <1.0 mmol/L (40 mg/dL) is recommended.

Treatment recommendations for older people.

The incidence and prevalence of atherosclerotic CV disease increases with age, which represents one of the non-modifiable risk factors for CVD. The proportion of people aged >65 years is increasing, and, as a consequence, the proportion of older subjects (even >85 years of age) experiencing myocardial infarction is growing significantly [14]. Furthermore, it is established that elevated cholesterol levels associate with increased CV mortality, independent of age. However, the use of statin therapy decreases with increasing age [15, 16], raising the question of how to treat older people properly. A recent meta-analysis of data from 27 randomized trials showed that statin therapy significantly reduced major vascular events, also participants older than 75 years of age [17]. Despite less clear evidence in the setting of primary prevention, these results support the use of statin therapy in older people. On the other hand, there are major concerns for the safety and adverse effects of statins in older patients due to the presence of co-morbidities and polypharmacy.

Based on all these considerations, the 2019 Guidelines, like those in 2016, recommend that older people with ASCVD be treated with statins in the same manner as younger patients (class I, A), however recommend a more cautious approach to reach the highest tolerable dose. However, the recommendations for primary prevention have changed. While the 2016 Guideline indicated that it was reasonable to treat primary prevention older patients with statin therapy (class IIa, B), especially those with a major risk factor, the new Guideline recommends statin therapy for primary prevention according to level of risk in those 75 years of age or younger and suggests that statin therapy may be considered for those >75 years of age if considered to be at high-risk or above. In the presence of renal impairment and/or the potential for drug interactions, statin therapy should be started at a low dose and then up-titrated to achieve the desired LDL-C goal (class I, C) [2].

Use of non-invasive imaging for ASCVD risk estimation.

Another update in the 2019 Guidelines not addressed in the 2016 document is a discussion of the use of atherosclerosis imaging to aid in ASCVD risk stratification**.** Coronary artery calcification (CAC) is reflective of atherosclerotic disease, is incrementally predictive of future cardiovascular events, independent of traditional risk factors, and can be quantified by computed tomographic imaging [18]. The presence of coronary calcium improves ASCVD risk discrimination and provides risk reclassification as compared to the use of traditional risk scoring systems in those thought to be at low- to moderate-risk. The absence of coronary calcium was found in the Multi-Ethnic Study of Atherosclerosis to be associated with lower fatal or non-fatal ASCVD risk of <5%, over a 10-year follow-up period, a finding that reclassifies patients otherwise considered to be at higher risk into the low-risk category. Conversely, those with scores of 100 Agatston units or greater have a 10-year risk of a least 7.5%, placing them into a high-risk category for which statin therapy provides therapeutic benefit. Non-invasive imaging to identify atherosclerotic plaque using carotid or femoral ultrasound has been demonstrated to be predictive of cardiovascular events, similar to coronary calcium,[19-23] and coronary CT angiographic evidence of a stenosis of >50% and information on plaque composition provide additional information that may result in upward risk reclassification.[24]

Lipoprotein (a) screening

An area of increased focus in the 2019 Guidelines is Lp(a), which is an independent risk factor for atherosclerosis [25]. Lp(a), which can freely cross the endothelial barrier, is easily retained within the arterial wall; moreover, it is believed to be pro-coagulant, due to its homology with plasminogen, and carries high levels of oxidized phospholipids, contributing to its pro-inflammatory effect in the arterial wall [26]. Circulating levels of Lp(a) are genetically determined.

Evidence from biology, epidemiologic studies, Mendelian randomization studies and genome-wide association studies has shown that elevated Lp(a) levels are associated with a higher risk of cardiovascular events[25, 26]. The 2016 Guidelines advised that Lp(a) was not recommended for screening in the general population, but that its measurement should be considered for those with premature cardiovascular

disease, FH, a family history of premature cardiovascular disease and/or elevated Lp(a), recurrent cardiovascular disease despite optimal lipid-lowering treatment, or a ≥5% 10 year risk of fatal CVD according to SCORE. The 2019 Guidelines have updated that recommendation to state that Lp(a) measurement should be considered at least once in each adult person's lifetime and stress the concept that subjects with very high inherited Lp(a) levels >180 mg/dL (>430 nmol/L) are at a lifetime risk of ASCVD equivalent to the risk associated with heterozygous familial hypercholesterolemia,[27], and might help in the reclassification of subjects who are borderline between moderate and high-risk (class IIa, C). No prospective trials of currently available lipid-lowering treatments have shown that drug-induced Lp(a) reductions are associated with ASCVD risk reduction. Two trials of PCSK9 inhibitors have demonstrated that in statin treated patients with ASCVD, high Lp(a) levels associate with higher absolute risk and thus greater treatment benefits.[28, 29] A non-randomised observational analysis of one of these trials suggested that reductions in Lp(a) in post ACS patients contribute to benefit independent of LDL-C lowering.[29] Two Mendelian randomization studies showed that a large absolute decrease in Lp(a) levels (65-100 mg/dL) is required to observe a CV risk reduction comparable to that obtained with a ~39 mg/dL (1 mmol/L) LDL-C level reduction [27, 30]. In addition, a 10 mg/dL genetically determined reduction of Lp(a) level was associated with a 5.8% lower risk of coronary heart disease, far less than that observed a similar genetically determined reduction of LDL-C (~14.5%) [27].

Treatment of hypertriglyceridemia

The 2016 Guidelines recommended that in those patients in whom secondary causes have been excluded, drug treatment should be considered for high-risk patients with triglycerides >2.3 mmol/L (200 mg/dL) (class IIa, B) and that statins are the first drugs to consider for CVD risk reduction in these patients (class IIa, B). Those who had triglycerides >2.3 mmol/L despite statin therapy should be considered for fenofibrate therapy (class IIb, C). The 2019 Guidelines modified these recommendations based on a large prospective RCT published in 2019.

The Reduction of Cardiovascular Events with Icosapent Ethyl‑Intervention Trial (REDUCE-IT) was an ASCVD outcomes placebo controlled trial in which statin-treated patients with fasting triglycerides of 1.52 to 5.63 mmol/L (135 to 499 mg/dL) with clinical ASCVD or diabetes mellitus and at least one additional risk factor were randomized to receive additive therapy with icosapent ethyl 4 grams daily or placebo.[4] Based upon the finding of a highly significant reduction in the primary endpoint, a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina, the key secondary endpoint, a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke, and a favorable safety profile, the Guidelines recommended that in high-risk (or above) patients with TG levels between 1.5 -5.6 mmol/L (135-499 mg/dL) despite statin treatment, the addition of icosapent ethyl 2 grams twice daily should be considered (class IIa, B). The use of bezafibrate or fenofibrate may be considered in high-risk, statin-treated patients who have triglyceride levels persistently >2.3 mmol/L (200 mg/dL) (class IIb, C). For primary prevention patients at LDL-C goal with triglycerides >2.3 mmol/L (200 mg/dL) despite statin therapy, the addition of bezafibrate or fenofibrate may be considered (class IIb, B).

Newer insights into statin intolerance

One of the major concerns of both clinicians and patients being considered for statin therapy is the potential for side effects, the most common of which are muscle related adverse effects [31]. These concerns lead to a reduced adherence to statin therapy and therapy discontinuation, which is of particular relevance in secondary prevention, or in high CV risk subjects. However, statin-induced severe muscle damage (myopathy or rhabdomyolysis) is a relatively rare event, as shown by randomized clinical trials, in which muscle symptoms are generally comparable between statin and placebo. In addition, statin intolerance is usually due to the nocebo effect [32]. Most of those people reporting a muscle-related adverse event while taking a statin can tolerate a re-challenge with a different statin, or with a lower statin dose, or with a regimen in which statin is taken less than daily[33-36].

Table S1. Cardiovascular Risk Categories according to the ESC/EAS Guidelines[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), stable angina, 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 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 T1DM of long duration (>20 years). • Severe CKD (eGFR <30 mL/min/1.73m^2). • A calculated SCORE ≥10% or 10-year risk of fatal CVD. • FH with ASCVD or with another major risk factor.
High-Risk	People with: • 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 mm Hg. • Patients with FH without other major risk factors. • Patients with DM without target organ damage,* with DM duration ≥10 years or another additional risk factor. • Moderate CKD (eGFR 30-59 mL/min/1.73m^2). • A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD.
Moderate-Risk	Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors. Calculated SCORE ≥1% and <5% for 10-year risk of fatal CVD.
Low-Risk	Calculated SCORE <1% for 10-year risk of fatal CVD.

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

*Target organ damage identified as microalbuminuria, retinopathy, or neuropathy.