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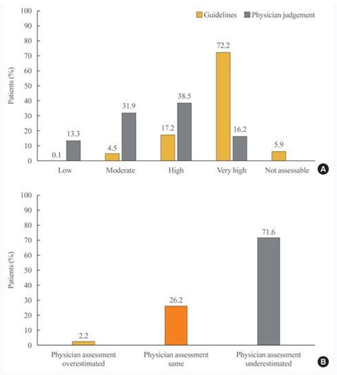
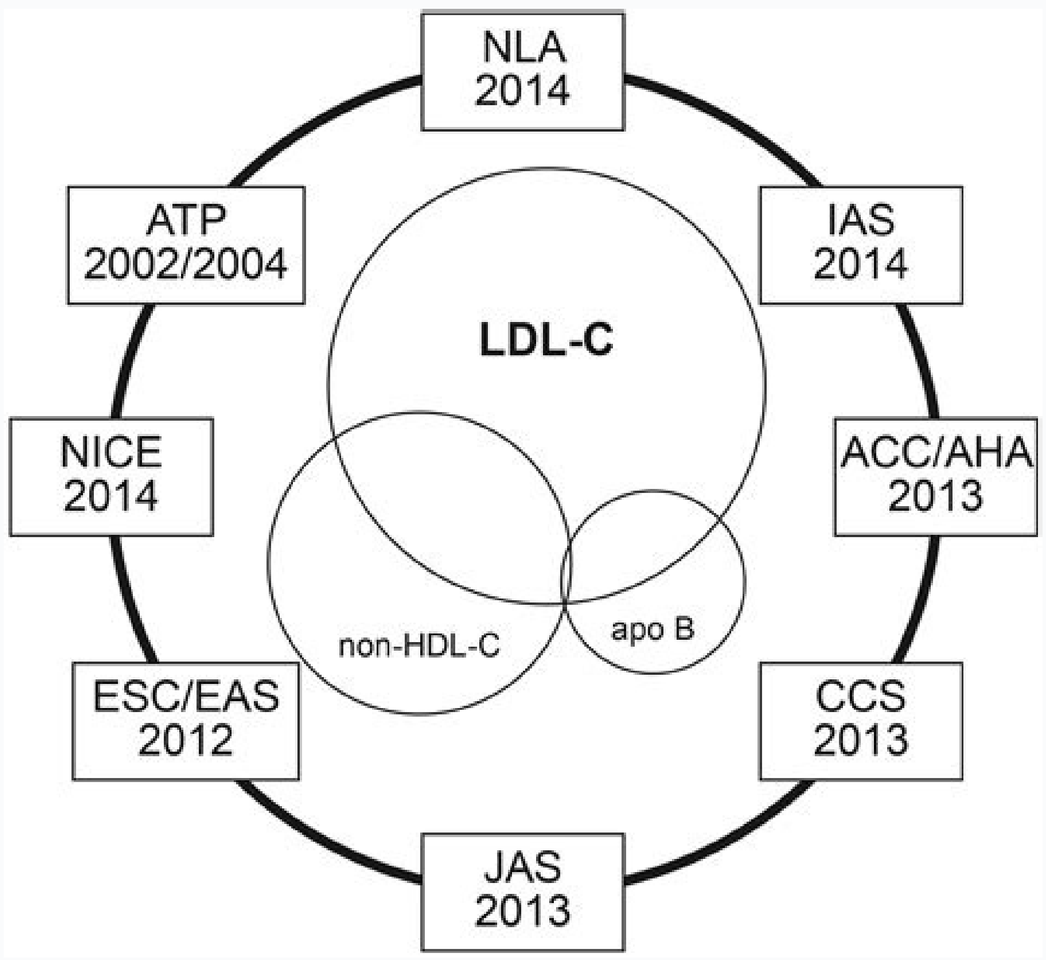


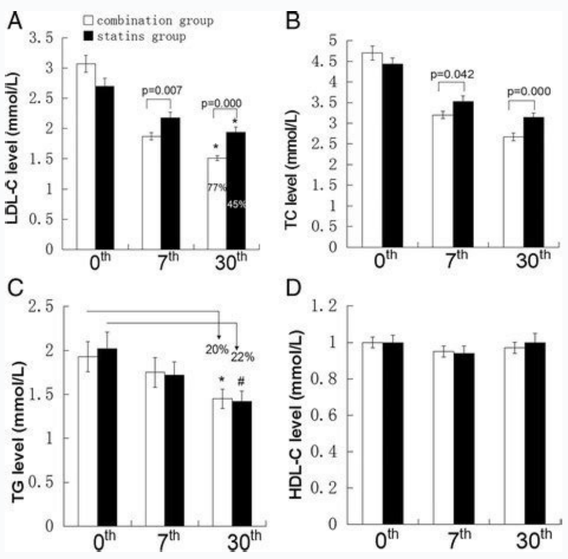
Table 1: Levels of total cardiovascular risk, goal LDL-c control levels and recommended treatment for each risk category*.

Lifestyle modifications are the milestone of health promotion and CVD risk reduction.		
Level of cardiovascular risk:	Goal LDL-c level*	Treatmen:
Very high CV risk: – Known cardiovascular disease†. – Type 1 diabetes and TOD‡. – Type 2 diabetes plus CVRF and/or TOD – Advanced chronic kidney disease (GF< 60 ml/min/1,73 m²). – SCORE ≥ 10%	< 70 mg/dl.	Intensive pharmacologic treatment with statins‖. Consider the association of ezetimibe if goal levels are not met.
High CV risk : – LDL–c ≥ 190 mg/dl, familial dyslipidemia or severe hypertension – Type 1 diabetes and/or type 2 diabetes with no CVRF nor TOD. – Moderate chronic kidney disease (GF < 30 ml/min/1.73 m²). – SCORE ≥ 5% and < 10%.	< 100 mg/dl.	Statins with appropriate lipid-lowering capacity to achieve goal levels. If these are not met with statins, consider the association with ezetimibe.
Moderate CV risk: – SCORE ≥ 1% and < 5%.	< 115 mg/dl.	The benefit of statin therapy is greater the higher SCORE punctuation is¶.
Low CV risk: – SCORE < 1%.	NE**.	NE**.

*: If triglycerides are over 400 mg/dl, non HDL cholesterol guidance is recommended (control goal levels are 30 mg/dl over LDL-c for each risk category).
†: Coronary artery disease (CAD) or ischemic stroke, periheral artery disease or carotid plaque
‡: Target organ damage (TOD).
§: Cardiovascular disease risk factor (CVRF).
‖: Intensive pharmacologic treatment = statins that can achieve LDL-c reduction over 50% (atorvastatin 40-80mg/day or rosuvastatin 20-40 mg/day). We must consider that elderly patients, CKD or those on polymedication (macrolides, fibrates…) are at increased risk of myopathy.
¶: Consider risk modifications (feasible from primary care) such as ankle-brachial index, family history, HDL-c.
**: No evidence (NE).

NO!





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Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS), Catapano AL, Reiner Z, De Backer G, Graham I, Taskinen MR, Wiklund O, Agewall S, Alegria E, Chapman MJ, Durrington P, Erdine S, Halcox J, Hobbs R, Kjekshus J, Perrone Filardi P, Riccardi G, Storey RF, Wood D; ESC Committee for Practice Guidelines 2008-2010 and 2010-2012 Committees. Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS), et al. Atherosclerosis. 2011 Jul;217 Suppl 1:S1-44. doi: 10.1016/j.atherosclerosis.2011.06.012. Atherosclerosis. 2011. PMID: 21723445 Review. No abstract available. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS), Catapano AL, Reiner Z, De Backer G, Graham I, Taskinen MR, Wiklund O, Agewall S, Alegria E, Chapman MJ, Durrington P, Erdine S, Halcox J, Hobbs R, Kjekshus J, Perrone Filardi P, Riccardi G, Storey RF, Wood D; ESC Committee for Practice Guidelines 2008-2010 and 2010-2012 Committees. Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS), et al. Atherosclerosis. 2011 Jul;217 Suppl 1:S1-44. doi: 10.1016/j.atherosclerosis.2011.06.012. Atherosclerosis. 2011. PMID: 21723445 Review. No abstract available. PDF Split View Article contents Figures & tables Video Audio Supplementary Data Die Deutsche Diabetes Dialyse Studie Scandinavian Simvastatin Survival Study ATP-binding cassette transporter 1 Action to Control Cardiovascular Risk in Diabetes Atherothrombosis Intervention in Metabolic syndrome with Low HDL-C/High Triglyceride and Impact on Global Health Outcomes Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6: HDL and LDL Treatment Strategies in Atherosclerosis Atorvastatin for Reduction of Myocardial Damage During Angioplasty CV risk estimation model from the Scottish Intercollegiate Guidelines Network A study to evaluate the Use of Rosuvastatin in subjects On Regular haemodialysis: an Assessment of survival and cardiovascular events Bezafibrate Infarction Prevention coronary artery bypass graft Cholesterol and Recurrent Events cholesterylester transfer protein carotid intima–media thickness COntrolled ROsuvastatin multiNational study in heart failure ESC Committee for Practice Guidelines Cholesterol Treatment Trialists' Collaboration cytochrome P450 isoenzyme Dalcetrapib Outcomes trial disability-adjusted life years diacylglycerol acyltransferase-2 European Atherosclerosis Society European Medicines Agency European Society of Cardiology Familial Atherosclerosis Treatment Study familial combined hyperlipidaemia Food and Drug Administration familial hypercholesterolaemia Fenofibrate Intervention and Event Lowering in Diabetes glomerular filtration rate Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Effect of rosuvastatin in patients with chronic Heart Failure Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Prevenzione G protein-coupled receptor highly active antiretroviral treatment HDL-Atherosclerosis Treatment Study high-density lipoprotein-cholesterol heterozygous familial hypercholesterolaemia human immunodeficiency virus hydroxymethylglutaryl coenzyme A homozygous familial hypercholesterolaemia Heart Protection Study 2 Treatment of HDL to Reduce the Incidence of Vascular Events high sensitivity C-reactive protein International Classification of Diseases intermediate-density lipoprotein Investigation of Lipid Levels Management to Understand its Impact in Atherosclerotic Events Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin Study lecithin-cholesterol acyltransferase low-density lipoprotein receptor low-density lipoprotein-cholesterol microsomal transfer protein monounsaturated fatty acid National Institute for Health and Clinical Excellence New York Heart Association peripheral arterial disease percutaneous coronary intervention proprotein convertase subtilisin/Kexin 9 peroxisome proliferator-activated receptor Pravastatin Pooling Project Prospective Cardiovascular Munster study Prospective Study of Pravastatin in the Elderly at Risk Pravastatin or Atorvastatin Evaluation and Infection Therapy polyunsaturated fatty acid renin–angiotensin–aldosterone system randomized controlled trial Randomized Evaluation of the Effects of Anacetrapib Through Lipid-modification Systematic Coronary Risk Estimation Simvastatin and Ezetimibe in Aortic Stenosis Study of Heart And Renal Protection systemic lupus erythematosus transient ischaemic attack Treating to New Targets Trial triglyceride-rich lipoprotein upstream transcription factor 1 Veterans Affairs High-density lipoprotein Intervention Trial very low density lipoprotein very low density lipoprotein-cholesterol World Health Organization Guidelines summarize and evaluate all available evidence at the time of the writing process on a particular issue with the aim of assisting physicians in selecting the best management strategies for an individual patient, with a given condition, taking into account the impact on outcome, as well as the risk–benefit ratio of particular diagnostic or therapeutic means. Guidelines are no substitutes but are complements for textbooks and cover the ESC Core Curriculum topics. Guidelines and recommendations should help physicians to make decisions in their daily practice. However, the final decisions concerning an individual patient must be made by the responsible physician(s).A large number of Guidelines have been issued in recent years by the European Society of Cardiology (ESC) as well as by other societies and organizations. Because of the impact on clinical practice, quality criteria for the development of guidelines have been established in order to make all decisions transparent to the user. The recommendations for formulating and issuing ESC Guidelines can be found on the ESC website (. ESC Guidelines represent the official position of the ESC on a given topic and are regularly updated.Members of this Task Force were selected by the ESC to represent professionals involved with the medical care of patients with this pathology. Selected experts in the field undertook a comprehensive review of the published evidence for diagnosis, management, and/or prevention of a given condition according to ESC Committee for Practice Guidelines (CPG) policy. A critical evaluation of diagnostic and therapeutic procedures was performed including assessment of the risk–benefit ratio. Estimates of expected health outcomes for larger populations were included, where data exist. The level of evidence and the strength of recommendation of particular treatment options were weighed and graded according to pre-defined scales, as outlined in Tables 1 and 2. Table 1Classes of recommendations Table 2 The experts of the writing and reviewing panels filled in declarations of interest forms of all relationships which might be perceived as real or potential sources of conflicts of interest. These forms were compiled into one file and can be found on the ESC website (. Any changes in declarations of interest that arise during the writing period must be notified to the ESC and updated. The Task Force received its entire financial support from the ESC without any involvement from the healthcare industry.The ESC CPG supervises and coordinates the preparation of new Guidelines produced by Task Forces, expert groups, or consensus panels. The Committee is also responsible for the endorsement process of these Guidelines. The ESC Guidelines undergo extensive review by the CPG and external experts. After appropriate revisions, it is approved by all the experts involved in the Task Force. The finalized document is approved by the CPG for publication in the European Heart Journal.The task of developing Guidelines covers not only the integration of the most recent research, but also the creation of educational tools and implementation programmes for the recommendations. To implement the guidelines, condensed pocket guidelines versions, summary slides, booklets with essential messages, and electronic version for digital applications (smartphones, etc.) are produced. These versions are abridged and, thus, if needed, one should always refer to the full text version which is freely available on the ESC website. The National Societies of the ESC are encouraged to endorse, translate, and implement the ESC Guidelines. Implementation programmes are needed because it has been shown that the outcome of disease may be favourably influenced by the thorough application of clinical recommendations.Surveys and registries are needed to verify that real-life daily practice is in keeping with what is recommended in the guidelines, thus completing the loop between clinical research, writing of guidelines, and implementing them into clinical practice.The guidelines do not, however, override the individual responsibility of health professionals to make appropriate decisions in the circumstances of the individual patients, in consultation with that patient, and, where appropriate and necessary, the patient's guardian or carer. It is also the health professional's responsibility to verify the rules and regulations applicable to drugs and devices at the time of prescription. 2. Introduction 2.1 Scope of the problem Cardiovascular disease (CVD) due to atherosclerosis of the arterial vessel wall and to thrombosis is the foremost cause of premature mortality and of disability-adjusted life years (DALYs) in Europe, and is also increasingly common in developing countries.1 In the European Union, the economic cost of CVD represents annually ~€192 billion1 in direct and indirect healthcare costs.The main clinical entities are coronary artery disease (CAD), ischaemic stroke, and peripheral arterial disease (PAD).The causes of these CVDs are multifactorial. Some of these factors relate to lifestyles, such as tobacco smoking, lack of physical activity, and dietary habits, and are thus modifiable. Other risk factors are also modifiable, such as elevated blood pressure, type 2 diabetes, and dyslipidaemias, or non-modifiable, such as age and male gender.These guidelines deal with the management of dyslipidaemias as an essential and integral part of CVD prevention.Prevention and treatment of dyslipidaemias should always be considered within the broader framework of CVD prevention, which is addressed in guidelines of the Joint European Societies' Task forces on CVD prevention in clinical practice.2–5 The latest version of these guidelines was published in 20075; an update will become available in 2012.These Joint ESC/European Atherosclerosis Society (EAS) guidelines on the management of dyslipidaemias are complementary to the guidelines on CVD prevention in clinical practice and address not only physicians [e.g. general practitioners (GPs) and cardiologists] interested in CVD prevention, but also specialists from lipid clinics or metabolic units who are dealing with dyslipidaemias that are more difficult to classify and treat. 2.2 Dyslipidaemias Lipid metabolism can be disturbed in different ways, leading to changes in plasma lipoprotein function and/or levels. This by itself and through interaction with other cardiovascular (CV) risk factors may affect the development of atherosclerosis.Therefore, dyslipidaemias cover a broad spectrum of lipid abnormalities, some of which are of great importance in CVD prevention. Dyslipidaemias may be related to other diseases (secondary dyslipidaemias) or to the interaction between genetic predisposition and environmental factors.Elevation of total cholesterol (TC) and low-density lipoprotein-cholesterol (LDL-C) has received most attention, particularly because it can be modified by lifestyle changes and drug therapies. The evidence showing that reducing TC and LDL-C can prevent CVD is strong and compelling, based on results from multiple randomized controlled trials (RCTs). TC and LDL-C levels continue therefore to constitute the primary targets of therapy.Besides an elevation of TC and LDL-C levels, several other types of dyslipidaemias appear to predispose to premature CVD. A particular pattern, termed the atherogenic lipid triad, is more common than others, and consists of the co-existence of

increased very low density lipoprotein (VLDL) remnants manifested as mildly elevated triglycerides (TG), increased small dense low-density lipoprotein (LDL) particles, and reduced high-density lipoprotein-cholesterol (HDL-C) levels. However, clinical trial evidence is limited on the effectiveness and safety of intervening in this pattern to reduce CVD risk; therefore, this pattern or its components must be regarded as optional targets of CVD prevention.Dyslipidaemias may also have a different meaning in certain subgroups of patients which may relate to genetic predisposition and/or co-morbidities. This requires particular attention complementary to the management of the total CV risk. 3. Total cardiovasular risk 3.1 Total cardiovascular risk estimation CV risk in the context of these guidelines means the likelihood of a person developing an atherosclerotic CV event over a defined period of time. Rationale for total cardiovasular disease risk All current guidelines on the prevention of CVD in clinical practice recommend the assessment of total CAD or CV risk because, in most people, atherosclerotic CVD is the product of a number of risk factors. Many risk assessment systems are available, and have been comprehensively reviewed, including Framingham, SCORE (Systemic Coronary Risk Estimation), ASSIGN (CV risk estimation model from the Scottish Intercollegiate Guidelines Network), Q-Risk, PROCAM (Prospective Cardiovascular Munster Study), and the WHO (World Health Organization).6,7Most guidelines use risk estimation systems based on either the Framingham or the SCORE projects.8,9In practice, most risk estimation systems perform rather similarly when applied to populations recognizably similar to that from which the risk estimation system was derived,6,7 and can be re-calibrated for use in different populations.6 The current joint European Guidelines on CVD prevention in clinical practice5 recommend the use of the SCORE system because it is based on large, representative European cohort data sets.Risk charts such as SCORE are intended to facilitate risk estimation in apparently healthy persons with no signs of clinical or pre-clinical disease. Patients who have had a clinical event such as an acute coronary syndrome (ACS) or stroke are at high risk of a further event and automatically qualify for intensive risk factor evaluation and management.Thus, although refined later in this chapter, very simple principles of risk assessment can be defined as follows5: SCORE differs from earlier risk estimation systems in several important ways, and has been modified somewhat for the present guidelines.Those withknown CVDtype 2 diabetes or type 1 diabetes with microalbuminuriavery high levels of individual risk factorschronic kidney disease (CKD)are automatically at VERY HIGH or HIGH TOTAL CARDIOVASCULAR RISK and need active management of all risk factors.For all other people, the use of a risk estimation system such as SCORE is recommended to estimate total CV risk because many people have several risk factors which, in combination, may result in unexpectedly high levels of total CV risk.The SCORE system estimates the 10 year risk of a first fatal atherosclerotic event, whether heart attack, stroke, or other occlusive arterial disease, including sudden cardiac death. Risk estimates have been produced as charts for high and low risk regions in Europe (see Figures 1 and 2). All International Classification of Diseases (ICD) codes that could reasonably be assumed to be atherosclerotic are included. Most other systems estimate CAD risk only. Open in new tabDownload slideSCORE chart: 10 year risk of fatal cardiovascular disease (CVD) in populations at high CVD risk based on the following risk factors: age, gender, smoking, systolic blood pressure, and total cholesterol. To convert the risk of fatal CVD to risk of total (fatal + non-fatal) hard CVD, multiply by 3 in men and 4 in women, and slightly less in old people. Note: the SCORE chart is for use in people without overt CVD, diabetes, chronic kidney disease, or very high levels of individual risk factors because such people are already at high risk and need intensive risk factor advice. Open in new tabDownload slideSCORE chart: 10 year risk of fatal cardiovascular disease (CVD) in populations at low CVD risk based on the following risk factors: age, gender, smoking, systolic blood pressure, and total cholesterol. To convert the risk of fatal CVD to risk of total (fatal + non-fatal) hard CVD, multiply by 3 in men and 4 in women, and slightly less in old people. Note: the SCORE chart is for use in people without overt CVD, diabetes, chronic kidney disease, or very high levels of individual risk factors because such people are already at high risk and need intensive risk factor advice.The new nomenclature in the 2007 guideline5 is that everyone with a 10 year risk of CV death of ≥5% has an increased risk. The reasons for retaining a system that estimates fatal as opposed to total fatal + non-fatal events are that non-fatal events are dependent on definition, developments in diagnostic tests, and methods of ascertainment, all of which can vary, resulting in very variable multipliers to convert fatal to total events. In addition, total event charts, in contrast to those based on mortality, cannot easily be re-calibrated to suit different populations.Naturally, the risk of total fatal and non-fatal events is higher, and clinicians frequently ask for this to be quantified. The SCORE data indicate that the total CVD event risk is about three times higher than the risk of fatal CVD for men, so that a SCORE risk of 5% translates into a CVD risk of 15% of total (fatal plus non-fatal) hard CVD endpoints; the multiplier is slightly higher in women and lower in older persons.Clinicians often ask for thresholds to trigger certain interventions, but this is problematic since risk is a continuum and there is no threshold at which, for example, a drug is automatically indicated, and this is true for all continuous risk factors such as plasma cholesterol or systolic blood pressure. Therefore, the targets that are proposed in this document reflect this concept. A particular problem relates to young people with high levels of risk factors; a low absolute risk may conceal a very high relative risk requiring intensive lifestyle advice. Therefore, a relative risk chart has been added to the absolute risk charts to illustrate that, particularly in younger persons, lifestyle changes can reduce relative risk substantially as well as reducing the increase in absolute risk that will occur with ageing (Figure 3). Open in new tabDownload slideAnother problem relates to old people. In some age categories the vast majority, especially of men, will have estimated CV death risks exceeding the 5–10% level, based on age (and gender) only, even when other CV risk factor levels are relatively low. This could lead to excessive usage of drugs in the elderly and should be evaluated carefully by the clinician.Charts are presented for TC. However, subsequent work on the SCORE database10,11 has shown that HDL-C can contribute substantially to risk estimation if entered as a separate variable as opposed to the ratio. For example, HDL-C modifies risk at all levels of risk as estimated from the SCORE cholesterol charts.10 Furthermore, this effect is seen in both genders and in all age groups, including older women.11 This is particularly important at levels of risk just below the 5% threshold for intensive risk modification; many of these subjects will qualify for intensive advice if their HDL-C is low.10 Charts including HDL-C are available as Addendum I to these guidelines on the ESC website (www.escardio.org/guidelines). The additional impact of HDL-C on risk estimation is illustrated in Figures 4 and 5. The electronic version of SCORE, HeartScore, is being modified to take HDL-C into account, and we recommend its use by using the www.heartscore.org in order to increase the accuracy of the risk evaluation. HeartScore will also include new data on body mass index (BMI). Open in new tabDownload slideRisk function without high-density lipoprotein-cholesterol (HDL-C) for women in populations at high cardiovascular disease risk, with examples of the corresponding estimated risk when different levels of HDL-C are included. Open in new tabDownload slideRisk function without high-density lipoprotein-cholesterol (HDL-C) for men in populations at high cardiovascular disease risk, with examples of the corresponding estimated risk when different levels of HDL-C are included.The role of a raised plasma TG level as a predictor of CVD has been debated for many years. Fasting TG levels relate to risk in univariate analyses, but the effect is attenuated by adjustment for other factors, especially HDL-C. More recently, attention has focused on non-fasting TG, which may be more strongly related to risk independently of the effects of HDL-C.12 Currently TG levels are not included in the risk charts. The effect of additional risk factors such as high sensitivity C-reactive protein (hs-CRP) and homocysteine levels was also considered. Their contribution to absolute CV risk estimations for individual patients (in addition to the older risk factors) is generally modest.The impact of self-reported diabetes has been re-examined. The impact of diabetes on risk appears greater than in risk estimation systems based on the Framingham cohort, with relative risks of ~5 in women and ~3 in men.In Figures 1–5 the approximate (~) equivalent values for TC are: mmol/L ~mg/dl 4 150 5 190 6 230 7 270 8 310 How to use the risk estimation chartsThe low risk charts should be considered for use in Belgium, France, Greece, Italy, Luxembourg, Spain, Switzerland and Portugal and also in countries which have recently experienced a substantial lowering of the CV mortality rates (see (CVD statistics) for recent mortality data). The high risk charts should be considered in all other countries of Europe. NOTE that several countries have undertaken national recalibrations to allow for time trends in mortality and risk factor distributions. Such charts are likely to represent current risk levels better.To estimate a person's 10 year risk of CVD death, find the table for their gender, smoking status, and age. Within the table find the cell nearest to the person's blood pressure and TC. Risk estimates will need to be adjusted upwards as the person approaches the next age category.Low risk persons should be offered advice to maintain their low risk status. While no threshold is universally applicable, the intensity of advice should increase with increasing risk.Relative risks may be unexpectedly high in young persons, even if absolute risk levels are low. The relative risk chart (Figure 3) may be helpful in identifying and counselling such persons.The charts may be used to give some indication of the effects of reducing risk factors, given that there will be a time lag before risk reduces and that the results of randomized controlled trials in general give better estimates of benefits. Those who stop smoking in general halve their risk.The presence of additional risk factors increases the risk (such as low HDL-C, high TG).The charts can assist in risk assessment and management but must be interpreted in the light of the clinician's knowledge and experience and of the patient's pre-test likelihood of CVD.Risk will be overestimated in countries with a falling CVD mortality, and underestimated in countries in which mortality is increasing.At any given age, risk estimates are lower for women than for men. This may be misleading since, eventually, at least as many women as men die of CVD. Inspection of the charts indicates that risk is merely deferred in women, with a 60-year-old woman resembling a 50-year-old man in terms of risk.Risk will also be higher than indicated in the charts in:Socially deprived individuals; deprivation drives many other risk factors.Sedentary subjects and those with central obesity; these characteristics determine many of the other aspects of risk listed below.Individuals with diabetes: re-analysis of the SCORE database indicates that those with known diabetes are at greatly increased risk; five times higher in women and three times higher in men.Individuals with low HDL-C or apolipoprotein A1 (apo A1), increased TG, fibrinogen, homocysteine, apolipoprotein B (apo B), and lipoprotein(a) [Lp(a)] levels, familial hypercholesterolaemia (FH), or increased hs-CRP; these factors indicate a higher level of risk in both genders, all age groups and at all levels of risk. As mentioned above, supplementary material (see Addendum I) illustrates the additional impact of HDL-C on risk estimation.Asymptomatic individuals with preclinical evidence of atherosclerosis, for example, the presence of plaques or increased carotid intima–media thickness (CIMT) on carotid ultrasonography.Those with impaired renal function.Those with a family history of premature CVD, which is considered to increase the risk by 1.7-fold in women and by 2.0-fold in men.Conversely, risk may be lower than indicated in those with very high HDL-C levels or a family history of longevity. 3.2 Risk levels A total CV risk estimate is part of a continuum. The cut-off points that are used to define high risk are in part arbitrary and based on the risk levels at which benefit is evident in clinical trials. In clinical practice, consideration should be given to practical issues in relation to the local healthcare and health insurance systems.Not only should those at high risk be identified and managed; those at moderate risk should also receive professional advice regarding lifestyle changes, and in some cases drug therapy will be needed to control their plasma lipids.In these subjects we should do all we realistically can to: Low risk people should be given advice to help them maintain this status. Thus, the intensity of preventive actions should be tailored to the patient's total CV risk.prevent further increase in total CV risk,increase awareness of the danger of CV risk,improve risk communication, andpromote primary prevention efforts.With these considerations one can propose the following levels of total CV risk:1. Very high riskSubjects with any of the following: 2. High riskDocumented CVD by invasive or non-invasive testing (such as coronary angiography, nuclear imaging, stress echocardiography, carotid plaque on ultrasound), previous myocardial infarction (MI), ACS, coronary revascularization [percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG)] and other arterial revascularization procedures, ischaemic stroke, PAD.Patients with type 2 diabetes, patients with type 1 diabetes with target organ damage (such as microalbuminuria).Patients with moderate to severe CKD [glomerular filtration rate (GFR) 2.3 mmol/L (more than ~200 mg/dL) who cannot lower them by lifestyle measures, and if the subject is at high total CV risk.The available pharmacological interventions include statins, fibrates, nicotinic acid, and n-3 PUFAs. As statins have significant effects on mortality as well as most CVD outcome parameters, these drugs are the first choice to reduce both total CVD risk and moderately elevated TG levels. More potent statins (atorvastatin, rosuvastatin, and pitavastatin) demonstrate a robust lowering of TG levels, especially at high doses and in patients with elevated TG. 8.2 Fibrates Mechanism of action Fibrates are agonists of peroxisome proliferator-activated receptor-α (PPAR-α), acting via transcription factors regulating various steps in lipid and lipoprotein metabolism. By interacting with PPAR-α, fibrates recruit different cofactors and regulate gene expression. As a consequence, fibrates have good efficacy in lowering fasting TG levels as well as post-prandial TG and triglyceride-rich lipoprotein (TRL) remnant particles. The HDL-C-raising effects of fibrates are modest.112 Efficacy in clinical trials The clinical benefits of fibrates in monotherapy are primarily illustrated by four prospective, randomized, placebo-controlled, clinical trials: Helsinki Heart Study (HHS), Veterans Affairs High-density lipoprotein Intervention Trial (VA-HIT), Bezafibrate Infarction Prevention study (BIP), and FIELD.124–127 The data from these trials have shown consistent decreases in the rates of non-fatal MI (although often as a result of post-hoc analyses), the effect being most robust in subjects with elevated TG/low HDL-C levels. However, the data on other outcome parameters have remained equivocal. Thus, the overall efficacy of fibrates on CVD outcomes is much less robust than that of statins. Recent meta-analyses reported that fibrate therapy reduced major CVD events by 13% [95% confidence interval (CI) 7–19], the benefits being most robust in patients with elevated TG levels (>2.3 mmol/L or more than ~200 mg/dl).52 Side effects and interactions Fibrates are generally well tolerated with mild side effects, gastrointestinal disturbance being reported in ~5% of the patients and skin rashes in 2%.128 In general, myopathy, liver enzyme elevations, and cholelithiasis represent the most well known safety issues associated with fibrate therapy.128 In the FIELD study, small but significant increases in the incidence of pancreatitis (0.8% vs. 0.5%) and of pulmonary embolism (1.1% vs. 0.7%), and a non-significant trend toward an increase in deep vein thrombosis (1.4% vs. 1.0%) were seen in those taking fenofibrate compared with placebo; this is in line with data from other fibrate studies.127Elevations of both CK (>5 times above the ULN) and ALT (>3 times above the ULN) were reported more frequently for patients on fenofibrate than on placebo, but the incidence of these abnormalities remained

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