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Editorial

Comments on the ESC Guidelines on Cardiovascular Disease Prevention (Version 2012). A Report of the Task Force of the Clinical Practice Guidelines Committee of the Spanish Society of Cardiology

Comentarios a la guía de práctica clínica de la ESC sobre prevención de la enfermedad cardiovascular (versión 2012). Un informe del Grupo de Trabajo del Comité de Guías de Práctica Clínica de la Sociedad Española de Cardiología

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INTRODUCTION

In line with Spanish Society of Cardiology (*Sociedad Española de Cardiología* [SEC]) policy on clinical practice guidelines,[1] the present article discusses novel, relevant or controversial aspects of the European Cardiology Society (ECS) guidelines on cardiovascular disease (CVD) prevention for 2012.

Methods

As proposed by the SEC clinical practice guidelines committee, the Hypertension and Preventive Cardiology and Rehabilitation sections selected a group of CVD prevention experts to review the ESC guidelines published in 2012 and translated in *Revista Española de Cardiología*. Their objective was to discuss the contents and appropriacy of the guidelines, analyze the method and highlight issues considered innovative, positive or questionable, as well as any left with no comment. The guidelines were divided into 5 parts and each was independently commented on by 2 experts. Based on their opinions, a document was prepared and, in turn, reviewed and approved by a group of experts designated by the SEC sections involved. All the experts have declared their conflicts of interest, which are stated in detail at the end of this article.

General Comments and Analysis of the Guidelines

Nearly 20 years have passed since 1994 when the European Society of Arteriosclerosis and the European Society of Hypertension published their first recommendations on CVD prevention. The present guidelines[2] represent the fifth revision of these recommendations and involved 9 scientific societies.

While there are undoubtedly important new ideas—especially on antithrombotic therapy and glycemic and antihypertensive control—the gap between the last 2 editions of the guidelines is less than that between previous editions and their predecessors.[3] The structure of the guidelines is innovative, aiming to respond to 5 basic questions (What is CVD prevention?, Why is CVD prevention needed?, Who should benefit from CVD prevention?, How should CVD prevention be used? and Where should CVD prevention programs be offered?). We have respected this structure when commenting on the guidelines.

1. WHAT IS CARDIOVASCULAR DISEASE PREVENTION?

Cardiovascular disease prevention is the application of measures aimed at the prevention and treatment of CVD. These guidelines use the customary ESC recommendations (class I, IIa, IIb, III; levels of evidence A, B and C) and, following World Health Organization recommendations, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) scale that, while mentioned in 2007, is explained more precisely and incorporated into each of the

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decision-making frames in the update. The strength of any recommendation is based on the level of evidence, risk-benefit ratio, patient preferences and available resources. A strong GRADE recommendation implies that most well-informed patients would opt for the intervention, most physicians would apply it, and the health care system would be able to provide it; a weak GRADE recommendation implies that some but not all patients would opt for the intervention, physicians would indicate it on an individual basis, and the healthcare system's capacity to provide it is questionable.

2. WHY IS CARDIOVASCULAR DISEASE PREVENTION NEEDED?

Cardiovascular disease prevention is fully justified on the grounds that CVD is the major cause of premature death in Europe. The guidelines highlight data from the MONICA (Multinational MONItoring of trends and determinants in CArdiovascular disease) study[4] and the IMPACT model,[5] showing that the fall in coronary disease is >50% due to treatment of cardiovascular risk factors (CVRFs) and 40% due to medication. Readers are referred to the National Institute for Health and Clinical Excellence report,[6] which shows how prevention reduces health care inequalities, prevents other illnesses as well as CVD and cuts costs by reducing mortality, events, treatment and productivity loss. All of this would justify CVD prevention from birth (if not earlier) and suggests we should consider its continuous, lifelong, population-wide application.

3. WHO COULD BENEFIT FROM CARDIOVASCULAR DISEASE PREVENTION?

Cardiovascular risk (CVR) should be determined in all asymptomatic adults with no evidence of CVD (IC, GRADE strong). Patients with CVD, diabetes and kidney disease (a highly novel concept), or markedly high CVRF, or target organ disease, and those with severe renal insufficiency are directly classified as very-high-risk patients (IC, GRADE strong); patients with a markedly high CVRF, those with diabetes with no other CVRF or target organ disease and those with moderate renal disease are considered as high-risk. High- or very high-risk patients are a priority for CVD prevention measures.

The guidelines insist on the use of multiple CVRF tables, such as the SCORE (Systematic COronary Risk Evaluation) tables (with a low-risk table for Spain) and stress that these predict fatal cardiovascular events. Fatal/non-fatal CVD risk can be calculated by multiplying fatal CVR by 3.

The use of these tables has some limitations. Age can lead to an inadequate interpretation of risk. In fact, much importance is given to relative vs. absolute risk, to avoid undertreating women and young persons and overtreating older people. Moreover, the risk tables do not include CVRFs such as cholesterol with high-density lipoprotein cholesterol (HDLc) (even though it is accepted that low values increase CVR in men and women, whether young or old). Calibrated country-specific risk calculations are available for countries like Spain.

An important innovation is the establishment of a very-high CVR category for patients with CVD, type 2 diabetes mellitus and 1 CVRF or target organ lesion, and severe chronic kidney disease (glomerular filtration rate <30 ml/min/1.72 m^2), and for those with SCORE >10%. The guidelines insist that the same criteria as those used in men should be applied to establish CVR in women and older people (IB, GRADE strong). In Spain, primary care physicians should calculate CVR. However, this is hampered by lack of time, leading to an underestimation of risk in many patients and their consequent undertreatment. Another problem is that all the tables include biochemical data, which entails not inconsiderable cost. Furthermore, the tables are based on multicenter studies in which women, young people and ethnic minorities are underrepresented. Another innovation is the concept of vascular age: the age of a person with equal risk but "ideal" CVRFs. The advantage of vascular age is that it need not be calibrated and can be used without taking into account baseline population risk.

One important new aspect is the minimal value attached to genetic studies (IIIB, GRADE strong) in CVR prediction given that while CVR does have a family association, the polygenic inheritance and the large number of determining factors mean it is not recommended. This does not, however, undermine the importance of a family history of hypercholesterolemia or ischemic heart disease (IHD), especially when first-degree family members aged <55 years (men) or <65 years (women) have IHD. Much importance is given to assessment of psychological and social factors and it is recommended they be assessed in the clinical interview (IIaB, GRADE strong). We believe that both detecting and treating these issues require substantial effort on the part of organizations, which is difficult to apply.

The biomarkers fibrinogen and C-reactive protein are again included and homocysteine and phospholipase A_2 associated with lipoprotein have been added. Use of these biomarkers is limited to moderate-risk patient reclassification in a higher risk group with a weak recommendation (IIb B, GRADE weak).

Imaging techniques are also included due to their value in detecting asymptomatic individuals with CVD, although the limited use of some techniques is recognized. The ankle-brachial index is recommended as is carotid intima-media thickness measurement (IIa B, GRADE strong) and computed tomography to determine coronary calcium (IIa B, GRADE weak), again aimed at individuals with moderate CVR. Although the ankle-brachial index is an indicator of peripheral arterial disease—even in asymptomatic individuals—and predicts CVR, recent analysis of the ARIC (Atherosclerosis Risk in Communities Study)[7] shows that ankle-brachial index measurement does not modify Framingham risk classification, hence we consider it should not be used systematically to assess CVR.

Carotid ultrasound is recognized as demonstrating the relation between disease severity at that level and the existence of disease in other vascular beds. However, when classical CVRFs are taken into account, carotid intima-media thickness alone provides little information. A recent meta-analysis indicates that investigating the existence of atheroma plaque increases the test's diagnostic precision.[8]

Coronary calcium is recognized as an indicator of coronary atherosclerosis. The Agatston score is an independent marker of coronary disease extent and prognosis, with a high negative predictive value (100% probability of not having significant stenosis for a value of 0), but provides no information about the degree of obstruction or lesion stability. Moreover, coronary atherosclerosis may not be associated with calcification. The calcium score improves risk classification, above all in moderate-risk patients,[9] but data on cost-effectiveness and radiation levels (usually <1 mSv) are still missing. We must remember that new dual technology scanners perform noninvasive coronary angiography with very little radiation (sometimes similar to that used in coronary calcium studies).

We consider imaging tests continue to have little practical application given that most are too expensive for general CVD screening. Specific guidance is needed on when they should be used and how patient management should be modified on the basis of the results obtained.

Other illnesses associated with higher CVR receive little attention—except for renal insufficiency, for which, according to the SHARP (Study of Heart and Renal Protection) study,[10] treatment similar to that of high-risk patients is recommended (IC, GRADE strong). Stratification and control of CVRFs in patients with obstructive sleep apnea/hypopnea (IIa A, GRADE strong) and in those with erectile dysfunction (IIa B, GRADE strong) is also recommended. Periodontitis continues to be described as a condition that raises CVR even though important confounding factors are recognized. Influenza vaccination is recommended in patients with CVD because it is associated with

reduced cardiovascular morbidity, although no level of recommendation is stated.

4. HOW CAN CARDIOVASCULAR DISEASE PREVENTION BE USED?

4.1. Lifestyle Changes

The guidelines emphasize the importance of lifestyle modification (IA, GRADE strong), supported by a broad base of scientific evidence, but offer no clear indications on how these interventions should be introduced into routine practice or who should apply them. The importance of cognitive-behavioral strategies and communication with the patient is stressed, when in Spain both cardiologists and primary care physicians are seriously limited by the consultation time available and, generally, have received little training in such techniques. The guidelines are inadequate in their approach to lifestyle changes and fail to show that these should be multidisciplinary and constant and that in secondary prevention this objective is best achieved in cardiac rehabilitation units.

4.2. Smoking

The gap between recommendations based on a broad range of evidence (IB, GRADE strong) and their poor implementation in daily clinical practice is made especially evident.

Emphasis on the importance of passive smoking and the legal restrictions on tobacco consumption in public places is new in this update. In Spain, the public smoking ban (Law 42/2010, January 2011) has already achieved substantial success with a fall in the prevalence of tobacco use. The impact of the law on the number of admissions for infarction or angina and its economic consequences remain to be seen.[11] We would have liked to see greater emphasis on the exemplary role of these laws as groups continue to lobby the Spanish government to have the current restrictions watered down.

The guidelines highlight the major impact of tobacco use on the risk of infarction in young people (5 times greater in smokers aged <50 years than in nonsmokers) and its growing prevalence in women. In Spain, the prevalence of tobacco use remains among the highest in Europe; smoking-related mortality is increasing in women but is falling among men. Moreover, smoking increases social inequalities in health care. The prevalence is greater in the population with lower income and educational levels and among those with less access to pharmacological aids for quitting smoking, which, while cost-effective, are not financed by the Spanish health care system.[12]

The efficacy and safety of nicotine substitutes is underlined although we would have preferred a clear statement that the most effective approach is to combine slow (patches) and fast (tablets or chewing gum) approaches. The recommendation on varenicline and bupropion use is overshadowed by safety warnings about the neurologic and psychiatric effects of both molecules and the cardiovascular consequences of varenicline use. The guidelines stress that the European Medicines Agency favors prioritizing the benefit of quitting smoking over the slight theoretical increase in risk of cardiovascular events with varenicline.

4.3. Nutrition

The sections on nutrition and obesity have little that is new, reflecting the paucity of new data in comparison with previous guidelines. Adopting the Mediterranean diet pattern is strongly preferred to any specific recommendations (IB, GRADE strong). The benefits of the DASH (Dietary Approaches to Stop Hypertension) diet for patients with high blood pressure (BP) are endorsed. In general, the guidelines reflect current evidence, which maintains that only alcohol consumption and, perhaps, body mass index (BMI) have a J-curve effect; other dietary recommendations are associated with CVR in a linear fashion. One noteworthy recommendation is that, due to the lack of results from clinical trials, neither excess homocysteine nor vitamin B or D deficiency should be treated. Finally, there is a remarkable lack of guidance on omega-3 fatty acid supplements—perhaps due to the lack of consistent data.

4.4. Physical Exercise

Relevant innovations are also lacking from this section. Recommendations on exercise intensity and duration are maintained but appropriate prescription and implementation of exercise in all patients with CVD go without comment. The safety of cardiac rehabilitation programs for patients with established CVD is emphasized. Greater insistence on the prescription of exercise as part of treatment should be included together with detailed recommendations on its frequency, duration and intensity; exercise prescription should be individually tailored and modified depending on individual patient progress. We would have liked to read comments on the possible benefits of more intensive exercise than that usually recommended or of interval training.

Healthy people are recommended they undergo medical examination including CVR assessment, baseline physical activity, and preferred exercise type, prior to commencing an exercise program. For patients with CVD, the safety of cardiac rehabilitation programs with supervised sessions in high-risk patients is emphasized.

4.5. Psychosocial Factors

This section includes the novel recommendation for psychological interventions to improve stress levels through a more healthy lifestyle. Although subanalyses have shown cardiovascular benefit associated with some antidepressant drug treatments (selective serotonin reuptake inhibitors), there is no evidence from studies specifically designed for this purpose. Moreover, the guidelines recognize a lack of evidence on the impact of anxiety on CVD incidence and prognosis.

4.6. Body Weight

Almost no new data have become available. The guidelines emphasize that overweight and obesity act independently as CVRFs and propose a BMI of 20-25 as the ideal. Overweight and obesity are the CVRFs that have developed worst in recent decades and the guidelines insist on the importance of weight reduction to reduce BP and lipids (IA, GRADE strong). The negative effects of obesity on the cardiovascular system (especially visceral adipose tissue) are effectively summarized.

Abdominal obesity represents greater CVR and waist circumference and waist:hip circumference ratio are the recommended measurements. Weight control is recommended when waist circumference is >94 cm (men) or >80 cm (women) and weight loss is recommended when it is >102 (men) or >88 cm (women).

Notably, the guidelines summarize evidence for the predictive value of different ways to measure excess weight, stressing that in clinical practice, BMI should not be abandoned in favor of waist circumference as both provide relevant information.

A short section is dedicated to confirming that in patients with CVD, obesity could entail better prognosis (the “obesity paradox”). We believe this is a complex and controversial issue. Longitudinal studies and detailed analyses of the development of weight have shown that obesity that persists over years is the principle determining factor in mortality from IHD. Moreover, many patients who die from CVD have a history of obesity in previous decades, which helps explain a high prevalence of CVRFs despite normal weight when CVD develops or death occurs.

Finally, orlistat and bariatric surgery are recognized as the only 2 currently-accepted, obesity-specific treatments. Both have advantages and disadvantages and should not be taken as substitutes for intensive modification of lifestyle and eating habits.

4.7. High Blood Pressure

These guidelines again represent a continuation of earlier versions. In practical terms, pulse pressure is losing importance and the use of suitably validated and calibrated automatic sphygmomanometers is accepted but professionals are explicitly advised not to use devices that measure BP on the finger or wrist.

Evidence for treating patients with grade 1 hypertension is scarce as most studies include high-risk patients.[13] After initiating nonpharmacologic measures, drug treatment can wait some weeks in moderate-risk patients with grade 2 hypertension, or months in those with grade 1 hypertension (IIa B, GRADE weak). An important innovation is the nonindication of treatment in patients with diabetes and high-normal blood pressure.

The guidelines maintain an eclectic position on treatment and insist on the importance of lowering BP without establishing first-line drugs. Here, the ESC guidelines differ from Joint National Committee-7 recommendations—the latter opting for thiazides[14]—and from the National Institute for Clinical Excellence guidelines[15]—which consider patient age when choosing treatment: angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB) for young people and calcium antagonists and diuretics for older patients.

For the first time a section is devoted to multiple treatments, and the combination of diuretics with ACE inhibitors or ARB, and ACE inhibitors with calcium antagonists is highlighted. Combining beta-blockers with diuretics is considered unfavorable due to adverse metabolic consequences, as is the combination of ACE inhibitors with ARB, due to increased secondary effects and the lack of proven clinical benefits. The recommended 3-drug therapy—needed in ≤15%-20% of patients with high BP—combines a renin-angiotensin system blocker, a calcium antagonist and a diuretic.[16] The position of beta-blockers remains unclear.

Another novelty is the change in objective BP due to the feeling that excessive BP reduction may be dangerous (J-curve phenomenon). The 2007 recommendation[17] to lower BP to <130 mmHg in patients with diabetes and in those with previous cardiovascular events is not maintained and optimal systolic and diastolic BP of 130-139 mmHg and 80-85 mmHg, respectively, is recommended. Normal values for ambulatory monitoring and self-management are specified although the reference for accepting these values is missing and studies are needed to support them. In high BP treatment in older patients, for the first time the benefits of treating patients aged >80 years is accepted, although it is recognized that this recommendation is based on studies in patients with systolic BP >160 mmHg. Renal artery ablation and the indications to study causes of secondary high BP are not discussed.

Treatment algorithms as a function of clinical variables are generally lacking and doubts remain as to whether recommended treatments can be extrapolated to Spain, where the prevalence of high BP associated with CVD is lower than in other countries.

4.8. Glycemic Control

In view of recent evidence on the risks associated with excessive glycemic control in patients with heart disease, the guidelines consider glycohemoglobin (HbA_{1c}) <7% (IA, GRADE strong) and HA_{1c} <6.5% sufficient in patients with a recent diagnosis in order to reduce long-term microvascular complications[18] (IIb B, GRADE weak). The American Heart Association (AHA) prevention guidelines for 2011[19] differ substantially. Their general objective is HbA_{1c} <7% or an even less aggressive target in patients with a history of hypoglycemia, established macrovascular or microvascular disease and the presence of other comorbidities or in those who cannot achieve the <7% objective despite intensive treatment. In our opinion, this focus is more practical as it reflects the fact that macrovascular disease causes more deaths in patients with diabetes than does microvascular disease, and that its prevention depends more on adequate control of the other CVRFs than on the intensity of glycemic control. Moreover, doubts exist on the safety of the over-ambitious objective in patients with advanced atherosclerosis due to the results of the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study, which was interrupted because of greater mortality in the intensive treatment branch. Both guidelines fail to clarify the role of HbA_{1c} in diagnosis and the prognostic implications for diabetes mellitus and prediabetes.

The recommendation of statin use in patients with diabetes is clear and independent of baseline cholesterol figures or the presence of CVD. Although the most frequent lipid abnormality in this group is diabetic dyslipidemia, the guidelines are firm on the role of statins, even though the benefit of fibrates is as yet unproven.

Both ESC and AHA guidelines propose metformin as the first-line therapy but we would have preferred a firmer stance on lifestyle changes. These guidelines do not recommend other treatments despite evidence of the cardiovascular safety of other anti-diabetic drugs such as thiazolidinediones or the importance of avoiding hypoglycemia in patients with macrovascular disease. Finally, they do not touch on the management of prediabetic patients, a highly prevalent situation among those with IHD.[20]

4.9. Lipids

The guidelines are clear on 3 issues: cholesterol and low-density lipoprotein cholesterol (LDLc) are major CVRFs; hypertriglyceridemia and low HDLc are independent CVRFs; and statins have a proven beneficial effect on CVD prognosis.

Measuring LDLc is recommended and the guidelines provide clear recommendations for different LDLc figures in different CVR situations (all GRADE strong). They detail different formulae to calculate LDLc and HDLc. However, the practical use of LDLc is not established and objective figures are not indicated. The lack of evidence of the beneficial effects of functional foods with lipid-lowering capacity is again recognized, as is the lack of prognostic evidence of the association of different lipid-lowering drugs.

4.10. Antithrombotic Treatments

This section offers changes with respect to the 2007 guidelines in regard to patients with established CVD. Following the Antithrombotic Trialists' (ATT) Collaboration meta-analysis, the use of acetylsalicylic acid is not recommended for primary prevention in any patients due to the increased risk of severe bleeding. Nor is the use of clopidogrel recommended. At the time of writing, several studies are assessing antiplatelet therapy in patients with diabetes and recent data support its benefits in patients with chronic kidney disease.[21]

In patients with established CVD, substantial scientific evidence has been incorporated showing the benefits of antiplatelet therapy with the new $P2Y_{12}$ receptor inhibitors prasugrel and ticagrelor, following acute coronary syndrome. Nothing new has been included on antithrombotic treatment in patients with atrial fibrillation and readers are referred to recent atrial fibrillation guidelines.

4.11. Treatment Adherence

This section is new and, in our view, impacts significantly on daily clinical practice. Adherence to treatment is low and the causes are multifactorial. The guidelines point to a possible solution by reducing the number of pills and discusses the "polypill" concept—for which

results have already been published—suggesting more in-depth assessment is needed before it can be recommended.

5. WHERE SHOULD CARDIOVASCULAR DISEASE PREVENTION PROGRAMS BE OFFERED?

For the first time this issue is approached on the basis of known studies and new consensus views expressed by experts or authorities. The guidelines particularly emphasize the need for different social, political and health care stakeholders to join forces in CVD prevention. In this context, the cornerstone Euroaction study[22] continues to figure large but we should remember that the measures it applied can be improved and are probably insufficient for some patient groups. Of the 6 studies cited in this section, 3 are expert statements, one is a registry, another a study parallel to the OASIS 5 (Fifth Organization to Assess Strategies in Acute Ischemic Syndromes) trial, and only 1 is trial-related with self-help anticoagulation therapy programs. Although interest in these programs is obvious, we believe that insufficient evidence has been provided to support the ESC recommendation (IIa B, GRADE strong); furthermore, there is no exact description as to what the programs entail.

Initiating prevention in infancy and maintaining it for life is recommended. The IIa B, GRADE strong level for this recommendation seems logical but is questionable since it is based on an AHA Declaration, which, although extensive and highly detailed, remains no more than expert opinion. We believe that a C level of evidence, which loses no strength, would be more appropriate. In this field, the need for directed clinical trials becomes evident.

The guidelines have at last highlighted the role of cardiac rehabilitation programs in a separate section. Although no new studies have appeared, we hope this spotlight will contribute to encouraging the creation of rehabilitation units across Spain. Cardiac rehabilitation programs have been unequivocally proven to reduce morbidity and mortality, making the dearth of such units in Spain and the tiny proportion of patients attending, all the more astonishing. Bearing in mind the limited human and economic resources, alternatives such as programs for low-risk patients coordinated by primary care physicians in a health center, or programs controlled by remote support, could be considered.

CONCLUSIONS

These guidelines represent a continuation of earlier editions in which known concepts are reinforced but they incorporate important innovations such as the GRADE classification system for recommendations, the definition of very high-risk patients, the change in HA_{1c} objectives, the importance of passive smoking, the updating of antiplatelet therapy in secondary prevention, the fact that antiplatelet drug treatment in primary prevention should no longer be indicated, and the need for a multidisciplinary approach in cardiac rehabilitation units coordinated by cardiologists, with the necessary implication of health care, political and social stakeholders.

CONFLICTS OF INTEREST

J.R. González Juanatey: consultancy and presentation (MSD, Rovi, Servier, Pfizer). I. Fernández Lozano: consultancy and presentations (Boston Scientific, Boehringer Ingelheim, Biotronik). J. López Sendón: consultancy and presentations (Daichi Sankio, Glaxo, AstraZeneca). F. Worner Diz: consultancy (MSD). I. Ferreira: consultancy and presentations (Bayer, MSD, Boehringer Ingelheim). M. Abeytua: attendance at scientific meetings not connected with the document (Biotronik). M. Pan: presentations (Lilly). E. Galve: consultancy (Boehringer Ingelheim, Novartis), presentations (Daichi Sankyo), administrative support (Pfizer).

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