Accepted author's manuscript. Published in final edited form as: European Journal of Clinical Investigation EJCI 2022 (in press). Publisher DOI: 10.1111/eci.13752

Invited Editorial to European Journal of Clinical Investigation

2021 European guidelines on cardiovascular prevention: challenges for an evidence-based patient care

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Keywords:

Guidelines, prevention, cardiovascular

Number of words:

1747

This year the European Society of Cardiology (ESC) presented its 2021 guidelines of cardiovascular (CV) prevention in clinical practice five years after the last update [1].

"Guidelines" are defined as an information intended to advise medical staff on how something should be done or what something should be done [2]. Several studies have shown that the implementation of guidelines were associated with an improvement of clinical outcomes and have demonstrated that guideline-driven medicine is also cost-reducing and increase physician satisfaction [3].

Unfortunately, still a high number of patients do not receive the quality of care they need and the control of CV risk factors remains suboptimal across several European countries [4].

Recently, patient-centered care has been considered to better understand patient's perspectives when recommendations are formulated [5] and to involve patients in evidence-based decisions making and in efficient care [6].

The new 2021 guidelines on CV prevention [1] described in an exhaustive manner and with a holistic approach how to intervene in clinical practice, both at the individual and population level, to reduce the burden of atherosclerotic cardiovascular diseases (ASCVD). Recommendations are classified according to the class of recommendation, being class I a "recommended or indicated", class IIa "should be considered", class IIb "may be considered" and class III as "not recommended". Level of evidence (Level A, B, and C) depends on the proportion of different data derivation: level A derived from multiple randomized clinical trials or meta-analyses, level B derived from a single randomized clinical trial or large non randomized studies, and level C as data derived from opinion of the experts and/or small studies, retrospective studies or registries.

At individual level, novel recommendations aim to estimate the 10-year risk of CV events for apparently healthy individuals according to three age groups (<50 years old, age between 50-69 years old, age ≥70 years old). Compared to 2016 ESC prevention guidelines where the Systemic Coronary Risk Estimation (SCORE) predicted 10-year risk of CV death in an overall range of age, the SCORE2 and SCORE2-OP recommended in the 2021 guidelines estimate an individual's 10-year risk of fatal and non-fatal CVD events with an adaptation of the predictive model according to the three age categories. Of note, patients with established ASCVD and/or diabetes, and/or moderate-to-severe renal disease and/or genetic/rarer lipid or BP disorders are considered at high or very high CVD risk, and they need treatment intensification (class of recommendations I, level of evidence B), with a stronger level of evidence (in general level of evidence A given the large trials). Those very-high risk patients were included preferably in clinical trials because their baseline features were more likely to increase the incidence of CV events and therefore the statistical power to show a superiority of an intervention over the study duration. In contrast, patients classified as low or moderate risk require lifestyle intervention in priority and the level of evidence to initiate pharmacological therapies remains weaker given the lack of dedicated trials.

For the first time, recommendations for older patients are discussed with more details in the guidelines. The estimated CV risk with these models give in general high-risk values even in apparently healthy people ≥70 years old. However, older individuals could also have multi-morbidity (> 3 chronic conditions), polypharmacy and be affected more by non-CV diseases (e.g. cancer or dementia). This

point has been considered, as for example treatment with statin at a low dose is recommended in people with ≥70 years who have a significant renal impairment and /or the potential for drug interactions (Class I, evidence C). In general, multi-morbid subjects have been excluded from clinical trials for many reasons (e.g. competitive risks, inability to follow-up, lack of adherence, side effects, and inability to give consent) and thus the level of evidence is still suboptimal in this population for treatment indication in primary prevention. The guideline acknowledge the lack of clear data evaluating the efficacy of statin in primary prevention in older patients. More definitive answers are expected with the results of the STAREE (STAtin Therapy for Reducing Events in the Elderly) and PREVENTABLE (Pragmatic Evaluation of Events and Benefits of Lipid-Lowering in Older Adults) trials.

The importance of lifetime risk assessment and treatment threshold is addressed in these guidelines to standardize as much as possible the process of care, but what is also remarkable is to consider individual cases. This terminology of shared decision making appears quite often in the current guidelines, to highlight the importance of multidisciplinary behavioral approach, including the patient and health care providers. Finally, to optimize CV risk management it is essential to promote a motivational interview, focusing on “what matters to you?” to better connect with patients, to improve drug adherence and to reach treatment goals. Motivational interviewing can also include a family member or a friend, particularly for older patients and it is a counseling method to change lifestyle habits and decreases CV risks.

In addition to established CV risk factors, there are potential risk modifiers to consider, such as psychosocial factors (Class of recommendation IIa, level of evidence B), ethnicity (Class of recommendation IIa, level of evidence B), frailty, polypharmacy and patient preferences (Class of recommendation IIa, level of evidence C). The routine collection of other potential modifiers, such as genetic risk scores, plasma and urinary biomarkers, or vascular tests or imaging methods (other than coronary artery calcium scoring or carotid ultrasound for plaque determination) is not recommended (Class III, level of evidence B).

At a population level, interventions on specific risk factors are encouraged in governmental restrictions and mandates (Class of recommendation I, level of evidence respectively A, B, C), media and education (Class of recommendation IIa, level of evidence C), economic incentives (Class of recommendation I, level of evidence B), schools (Class of recommendation I, level of evidence B), worksites and community setting (Class of recommendation IIa, level of evidence C), including measures to reduce air pollution (Class of recommendation I, level of evidence C). Compared to individual recommendations, population recommendations are not based on clinical trials but rather on expert opinion or health policy decision.

Overall summary of class of recommendations and underlying scientific evidence

In addition to evaluating the content and the global picture of the guidelines, the analysis of the patterns of the recommendations in the guidelines are important to understand the source of scientific evidence and to define the gaps in knowledge in specific era. This approach would help to critically consider each recommendation. In 2021 ESC prevention guidelines, most of the recommendations belong to the class I (57%), as they are “recommended or indicated”, 22% belong to Class IIa (“should be considered), 16% to Class IIb (“may be considered”) and only 5% (9/177) belong to class III (“it is not recommended”) (**Table 1**). The 5% of class III recommendations in the guidelines could be explained because neutral

or negative results are less frequently published than clinical trials with positive results. Alternatively, neutral trials are less likely to be cited in the guidelines than positive trials [7]. It remains also questionable whether more recommendations should highlight contra-indicated therapies or therapies that make harm or are ineffective. In parallel, the scientific evidence needs probably to be strengthened with research aiming to discontinue therapies in subgroups with high vulnerability or in population with comorbidities. For instance, recommendations are now less supportive for the use of aspirin in the older patients in primary prevention or in case of high-risk of bleeding after coronary intervention (to shorten dual antiplatelet duration). In these guidelines, class III recommendations do not advise to initiate a combination of angiotensin converting enzyme inhibitors and angiotensin receptor blocker treatments, or statin therapy in premenopausal female patients who are considering pregnancy, or are not using adequate contraception, or in patients with dialysis-dependent chronic kidney disease who are free of ASCVD.

The recommendations that are not based on strong level of evidence from multiple RCTs or a single large RCT are more likely to disappear or down-graded in the future [9]. This important issue was already pointed out in previous guidelines from the ESC and from the American Heart Association (AHA) [8], where the durability of recommendations depends on the levels of evidence. As expected, 53/101 (52%) of class I recommendations have the highest level of evidence and are derived from multiple randomized clinical trials (RCTs) or meta-analyses, whereas this proportion decreased to 5/39 (13%) among class IIa recommendations and to 4/28 (14%) among class IIb recommendations.

There are 21 over 101 recommendations classified as class I, but with low level of evidence (21% of class I recommendations have a level of evidence C). In general, recommendations for policy interventions at the population levels are mostly of level of evidence C (e.g., governmental restrictions and mandates, education, schools setting, worksites, community settings,…), mainly because the feasibility to perform RCT is more challenging at population level.

In conclusion, some questions are pointed out to stimulate debate and thoughts on the complexity of guidelines elaboration:

- Do we need more Class III recommendations to describe therapies that are ineffective or even harmful?
- Why certain subjects are under-represented in some RCTs? Why are some relevant clinical questions not answered or confirmed with more trials? Some important questions are unlikely to be funded by industries, therefore those efforts need to be supported by scientific societies or other funding agencies.
- How much is the concept of “patient-centered care” taken in consideration on writing guidelines? Should we include one patient in the guidelines committee to represent the point of view of patients? Do we need to ask health care providers to determine the topics where specific guidance is needed to improve the care of their patients?
- The balance between CV disease risk assessment and treatment threshold remains a matter of individual consideration and shared decision-making. What are the key elements that guide the discussions between the patients and the health care providers? At which degree health care

provers are influenced by financial interests, academic credentials, relation with industry, or constraints from health-deciders or politics in their practice?

Table 1: class of recommendations and level of evidence of all 177 recommendations

	Level of evidence			**Total**
Classes of recommendations	**A**	**B**	**C**	
Class I	53/101 (52%)	27/101 (27%)	21/101 (21%)	101/177 (57 %)
Class IIa	5/39 (13%)	26/39 (67%)	8/39 (21%)	39/177 (22%)
Class IIb	4/28 (14%)	14/28 (50%)	10/28 (36%)	28/177 (16%)
Class III	3/9 (33%)	4/9 (44%)	2/9 (22%)	9/177 (5%)
Total	65 /177 (37%)	71/177 (40%)	41/177 (23%)	177 (100%)

Conflicts of interest

Authors do not report conflicts of interest regarding the content of this article.

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