Vojislav Giga[1,2], Marija Petrović[1]

PRIMARY PREVENTION OF CARDIOVASCULAR DISEASES: DIFFERENCES BETWEEN EUROPEAN AND UNITED STATES GUIDELINES

Abstract: European Society of Cardiology guidelines on primary prevention of cardiovascular diseases were published in 2016. Those guidelines are to some extent different from current set of American College of Cardiology/ American Heart Association guidelines dealing with primary prevention. Both United States and European guidelines agree that primary prevention of cardiovascular diseases is essential. Guidelines ask for individual risk calculation and agree that LDL-cholesterol is directly related to cardiovascular disease morbidity and mortality and should be adequately treated. However, there is substantial difference in risk estimation and treatment strategies in patients without established cardiovascular disease. The purpose of this short review is to underline similarities and especially difference between current primary prevention guidelines in United States and Europe, and to address advantages and disadvantages of each of these strategies.

Introduction

European Society of Cardiology (ESC) released recently new version of guidelines on cardiovascular (CV) disease prevention in order to further decrease CV morbidity and mortality in Europe (1). In 2013 American Colleague of Cardiology/ American Heart Association (ACC/AHA) has published three different papers dealing with CV prevention: assessment of CV risk (2), lifestyle modification to reduce CV risk (3) and the third paper on treatment of high cholesterol levels (4).

Risk estimation

The initial approach of risk management is to establish individual risk for CV events and to start optimal treatment (life style changes with or without pharmacolo-

[1] Cardiology Clinic, Clinical Center of Serbia, Visegradska 26, 11 000 Belgrade, Serbia. E-mail: voja2011@yahoo.com
School of Medicine, University of Belgrade, Koste Todorovica 2, Belgrade, Serbia;

[2] Cardiology Clinic, Clinical Center of Serbia, Visegradska 26, Belgrade, Serbia.

gical treatment) based on this calculation. Both, in European and American, guidelines high risk patients are considered as those with established CV disease, diabetes and familial hypercholesterolemia. ESC guidelines consider patients with chronic kidney disease as being (very) high risk patients, whereas in ACC/AHA guidelines CKD patients are not discussed at all. Those high risk patients, according to all available data, require strict risk factor control in order to avoid further adverse events and disease progression.

In all other patients risk should be assessed using global risk calculator. From 2003, ESC guidelines use SCORE charts to calculate individual 10 years risk of first fatal CV event. SCORE charts are based on huge European dataset of more than 200000 patients that have been externally validated (5) for low risk and high risk countries (such as Serbia). Fatal CV events are defined as death due to coronary artery disease, stroke and abdominal aneurism. CV risk is calculated based on the age, gender, smoking status and levels of total cholesterol or total/HDL cholesterol ratio and systolic blood pressure (1). US guidelines recommend Pooled Cohort Studies Equation (PCSE) (based on the results of 4 cohorts) for the calculation of CV risk using similar variables as SCORE with addition of race, HDL cholesterol, treatments of hypertension and diabetes (2). However, the major difference between two guidelines is that US guideline uses 10 years risk of any first CV event rather than fatal CV event. From epidemiological point of view it doesn't seem appropriate to use the end point of natural history of the disease as a target for primary prevention as in ESC guidelines. The authors of the guidelines should keep in mind that practitioners in their every-day work want to prevent the disease and not only the death from the disease. Also, in many European countries mortality from CV diseases is decreasing so the SCORE-based treatment (especially statin use) might be omitted in spite of high CV disease morbidity (6).The authors of ESC guidelines used mortality rather than morbidity deliberately. There were several reasons for this decision: Death is completely reproducible hard end-point event that is not variable and dependent upon various definitions, diagnostic criteria and diagnostic tests like myocardial infarction; it is obvious that increased risk of CV death is related to increased risk of non-fatal events. The SCORE data indicate that the total CV event risk is about three times higher than risk of CV death in men, four times higher in women and less than three times in older persons in whom first event tend to be more frequently fatal (7).Third, using only fatal events enable easy recalibration of the model if needed. The other reason for the use of CV death in SCORE lies in the fact that model is based on old cohorts from 1972 to 1991 year, with death certificates being the most consistent data source at that time.

The second important limitation of ESC guidelines is that SCORE risk is applicable only in age range from 40 to 65 years. The intention was to avoid overtreatment of older subjects due to the high impact of age on overall risk assessment, even though

other risk factors are reasonable low in those patients. Based on US guidelines almost to all subjects older than 70 years, according to risk calculator moderate to high-intensity treatment should be prescribed. However, those physicians who advocate for ESC guidelines approach should keep in mind that only 18% of all fatal CV events in apparently healthy people occur in the age group of 40-65 years (8). Contemporary ESC guidelines do not contain an information how to treat elderly people without apparent CV disease, although it is known that some preventive measures can postpone morbidity and mortality in this age group.

The use of different risk calculators SCORE vs. PCSE as it has been shown previously results in different risk estimation (9). Obviously US risk calculator by assessing both fatal and nonfatal events results in higher estimation of risk. According to US guidelines patients with 10 years risk of 7.5% for first fatal or non-fatal event are considered to be high risk patients and require intense risk factor management, including statins. However, the 10 years risk of 7.5% corresponds to a 2.5% risk of CV death in next 10 years in the SCORE model that is considered as moderate risk. The recent analysis of Multi-Ethnic Study of Atherosclerosis demonstrated that US risk score overestimates risk of endpoints by 78%(10). From practical point of view the most important question is how this risk estimation affects primary prevention of CV morbidity and mortality.

Consequences of different risk calculation models

The first consequence of ACC/AHA guidelines acceptance is significant increase in statin use. Consistent data including two recent meta-analysis, showed beneficial effect of statin use in primary prevention on CV morbidity and mortality (11,12). So the question is not whether statins should be used in persons without established disease, rather to identify adequate patients who will benefit most from statin use. It is estimated that adherence to American guidelines would dramatically increase the number of patients eligible for statin treatment, with 12.8 million of new statin users in USA(13). This number is primarily related to increased statin use among older adults (over 70 years) without CV disease (i.e. in the group of patients in whom the data on mortality reduction with statin are not so definite). Recently, on 7229 individuals free of CV disease, aged 45-75 years, examined between 1997 and 2008. for the Rotterdam study was shown that need for statin treatment is significantly higher when using US instead of ESC guidelines. The ACC/AHA recommends statin in 4284 (58%) participants, while ESC guidelines recommend it in 2399 participants (33%), with huge overlapping by 95.8% with American guidelines. In majority of cases with difference between two guidelines statin treatment is suggested by US guidelines, whereas is inappropriate by ESC guidelines. However, there is small group of patients (0.8%) at very high risk who are eligible by ESC, but not ACC/AHA guidelines. Those are

patients with chronic kidney disease and significantly reduced renal function, as well as patients with heart failure who are not mentioned in US guidelines at all (14).

Higher prescription of statin according to US guidelines would have two important effects. First, it would increase cost of treatment, that is an issue especially important for countries with low income (such as Serbia). Second, such a broad use of statin in primary prevention would increase statin related side effects, especially among older subjects. These adverse effects include myopathy (with potentially fatal rhabdomyolysis) and liver damage. A much more important adverse effect is increase in new cases of diabetes mellitus, that has been estimated to range from 9-13% of new cases of diabetes with prolonged statin treatment (15-17). Importantly, it has been shown that new occurrence of diabetes is dose dependent adverse effect (18).

The other crucial difference between US and ESC guidelines is that last issue of US guidelines doesn't define therapeutical goal for LDL-cholesterol. According to calculated risk patient should be offered moderate of intensive statin treatment. This approach is not something that practitioners are used to. In majority of cases doctors start treatment with lower statin dose with further adjustment based on LDL-cholesterol levels. As opposite, ACC/AHA guidelines may unintendedly result in „fire and forget" approach, with prescribing appropriate dose but without further follow up. It has been clearly shown that this approach leads to worse adherence of patients and worse CV outcome due to lesser degree of cholesterol reduction (19) . Adherence to life-long statin treatment is problem per se, since 50% of all patients with prescribed statin and 75% of those who were prescribed statin for primary prevention stop taking the drug within one year of treatment initiation (20).

It should be clearly stated that US guidelines recommend assessment of therapeutic response and possible side effects 4 to 12 weeks after the beginning of treatment and every 3 to 12 months thereafter (4). However it remains unclear what doctor should do with such information if the goal of treatment is not define. One should be aware, that this approach may cause problem for general practitioners when in need to treat hypercholesterolemia and to communicate risk to the patients. It is of note that current prevention guidelines from both sides of Atlantic ocean are not designated only for cardiologist but even more to general practitioners, who seeks for easy to use and clear guidelines in order to facilitate every day practice.

Conclusion

Both US and ESC guidelines have some advantages in disadvantages as discussed earlier. Before some consensus between associations is made, it seems prudent to promote application of European guidelines in Serbia. SCORE risk estimation despite of certain limitations is based on European population, similar to ours, although the best approach would be recalibration of the SCORE model according to

national CV mortality statistics. The basic principles of risk estimation and patient treatment as recommended by ESC guidelines are more acceptable for our medical practitioners especially in terms of clear goals of treatment. Also, adherence to US guidelines would significantly increase the costs of treatment due to increase statin prescription. One should always keep in mind that Guidelines provide only the framework for patient treatment but definite decision should be based on patients characteristics and preferences. Effort should be made to improve patients adherence in primary prevention settings.

References:

1. Piepoli MF, Hoes AW, Agewall S et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR).Eur Heart J 2016; 37: 2315–81.
2. Goff CD, Lloyd-James DM, Bennett G et al. 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk. J Am Coll Cardiol 2014; 63: 2935–59.
3. Eckel RH, Jakicic JM, Ard JD et al. 2013 ACC/AHA Guideline on the Lifestyle Management to Reduce Cardiovascular risk. J Am Coll Cardiol 2014; 63: 2960–84.
4. Stone NJ, Robinson JG, Lichtenstein AH et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation, 2014; 129: S1–S45.
5. Atkas MK, Ozduran V, Pothier CE, Lang R, Lauer MS. Global risk scores and exercise testing for predicting all-cause mortality in preventive medicine program. JAMA 2004; 292: 1462–1468.
6. Mortensen MB, Falk E. Limitations of the SCORE-guided European guidelines on cardiovascular disease prevention. Eur Heart J 2016; 1: 1–5.
7. Van Dis I, Geleijnse JM, Boer JM et al. Effects of including nonfatal events in cardiovascular risk estimation, illustrated with data from The Netherlands. Eur J PrevCardiol 2014; 21: 377–383.
8. Mortensen MB, Afzal S, Nordestgaard BG, Falk E. The high-density lipoprotein adjusted SCORE model worsens SCORE-based risk classification in the contemporary population of 30824 Europeans: the Copenhagen General Population Study. Eur Heart J 2015; 36: 2446–2453.
9. Reiner Z. Similarities and differences between European and United States guidelines for the management of dyslipidemias. KardiologiaPolska 2015; 73: 471–477.
10. DeFilippis AP, Young R, Carrubba CJ et al. An analysis of calibration and discrimination among multiple cardiovascular risk scores in a modern multiethnic cohort. Ann Intern Med 2015; 162: 266–275.

11. Mihaylova B, Emberson J, Blackwell L, et al; Cholesterol Treatment Trialists' (CTT) Collaborators. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet 2012; 380: 581–590.
12. Taylor F, Huffman MD, Macedo AF, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev 2013; 1: CD004816.
13. Pencina MJ, Navar-Boggan AM, D'Agostino RB Sr et al. Application of new cholesterol guidelines to a population-based sample. N Engl J Med 2014; 370: 1422–1431.
14. Pavlovic J, Greenland P, Dockers JW et al. Comparison of ACC/AHA and ESC guideline recommendation following trial evidence for statin use in primary prevention of cardiovascular disease. Results from population based Rotterdam Study. JAMA 2016; 1: 708–713.
15. Rajpathak SN, Kumbhani DJ, Crandall J et al. Statin therapy and risk of developing type 2 diabetes: a meta-analysis. Diabetes Care 2009; 32: 1924–1929.
16. Sattar N, Preiss D, Murray HM et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet 2010; 375: 735–742.
17. Culver AL, Ockene IS, Balasubramanian R et al. Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative. Arch Intern Med 2012; 172: 144–152.
18. Cederberg H, Stančáková A, Yaluri N et al. Increased risk of diabetes with statin treatment is associated with impaired insulin sensitivity and insulin secretion: a 6 year follow-up study of the METSIM cohort. Diabetologia 2015; 58: 1109–1117.
19. Wei L, MacDonald TM, Watson AD et al. Effectiveness of two statin prescribing strategies with respect to adherence and cardiovascular outcomes: observational study. Pharmacoepidemiol Drug Saf 2007; 16: 385–392.
20. Jackevicius CA, Mamdani M, Tu JV. Adherence with statin therapy in elderly patients with and without acute coronary syndromes. JAMA 2002; 288: 462–467.