Polish Forum for Prevention Guidelines on the so-called new cardiovascular risk factors and markers, which have a potentially significant role in the strategy for the prevention of cardiovascular diseases

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Introduction

The large case-control study INTERHEART [1], which enrolled over 15 thousand patients from every inhabited continent, showed that nine modifiable risk factors accounted for at least 90% of the risk of myocardial infraction, which suggested that the role of additional risk factors in the prediction of coronary events was minor. However, it is estimated that about 20% of patients with cardiovascular events do not have any of the main cardiovascular risk factors and 50% have only one of them [2].

So far about 200 new risk factors have been identified. Many of them do not have standardized methods of measurement or are not associated with cardiovascular risk independently of the main cardiovascular risk factors.

The search for new plasma risk factors which could improve detection of subjects at risk of atherosclerosis and its thromboembolic complications was bi-directional and comprised:

1) assessment of the markers of inflammation and endothelial function, because atherogenesis is a chronic inflammatory process of the arterial wall,
2) assessment of the markers of activation of thrombosis and fibrinolysis, because myocardial infarction and ischaemic stroke are consequences of thromboembolic processes.

The so-called new risk factors for which the most reliable evidence of their association with the risk of cardiovascular events is available [3] are as follows.

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Serologic factors

1) lipid risk factors:
   a) apolipoprotein B (Apo B)
   b) lipoprotein (a) [Lp(a)]
   c) lipoprotein-associated phospholipase A2 (Lp-PLA2)
   d) oxidised LDL
2) inflammatory risk factors:
   a) C-reactive protein (CRP)
   b) serum amyloid A (SAA)
   c) interleukin 6 (IL-6) and interleukin 18 (IL-18)
   d) CD40 ligand
   e) myeloperoxidase
3) homocysteine
4) asymmetric dimethylarginine (ADMA)
5) matrix metalloproteinase 9 (MMP-9)
6) tissue inhibitor of metalloproteinase 1 (TIMP-1)
7) glutathione peroxidase activity

Structural and functional risk factors

1) intima-media thickness of carotid arteries (IMT)
2) coronary calcium score
3) arterial stiffness
4) brachial-ankle index
5) endothelial dysfunction
6) albuminuria

Haemostatic risk factors

1) fibrinogen
2) D-dimer
3) tissue plasminogen activator – tPA and plasminogen activator inhibitor 1 (PAI-1)
4) von Willebrand factor (vWF)

Regarding the current guidelines of the European Society of Cardiology, American Heart Association and American College of Cardiology, it is not recommended to assess the so-called new risk factors in order to improve prediction of cardiovascular risk.

No methods of clinically significant modification of these factors are currently available.

It is unlikely that one new risk factor will improve prediction models based on the traditional risk factors, whose position is invariably strong. It is probable however that in the future a panel of biomarkers will be available, which will make possible an individualized approach to the therapy of cardiovascular diseases.

Guidelines

1. **Haemostatic factors.** The following factors have been shown to increase cardiovascular disease (CVD) risk: fibrinogen (an increase in plasma fibrinogen concentration of 1 g/l increases the risk of CVD incidence twofold), clotting factor VII, von Willebrand factor (vWF), plasminogen activator inhibitor (PAI-1), tissue plasminogen activator (tPA). These factors can usually be improved by standard preventive interventions. In some conditions it is justified to introduce pharmacological treatment that influences the haemostatic system as a preventive tool. Currently no specific intervention aimed at reduction of CVD risk by modulating the aforementioned haemostatic factors in the general population is available and their routine measurement to estimate CVD risk is not recommended.

2. **Inflammatory markers.** Elevated plasma levels of CRP >3 mg/dl increase the risk of CVD events by about 50%. Higher CVD risk has also been attributed to some other inflammatory markers such as: interleukins (IL-6, IL-10, IL-18), tumour necrosis factor α (TNF-α), soluble CD40 ligand (sCD40L), matrix metalloproteinase 9 (MMP-9), myeloperoxidases. In clinical practice it is not recommended to measure the aforementioned inflammatory markers in order to estimate CVD risk.

3. **Homocysteine.** Homocysteine plasma levels elevation of 3 µmol/l increases the risk of coronary heart disease and stroke by about 11–30% and about 20% respectively. A diet including at least 400 µg of folic acid per day reduces blood homocysteine concentration; however, no beneficial effect of folic acid supplementation on CVD risk has been achieved. In clinical practice it is not recommended to measure the homocysteine level in order to estimate CVD risk.

4. **Imaging methods** such as B-mode ultrasound measurement of intima-media thickness and endothelium dependent dilation of the vessel wall as well as a quantitative assessment of artery calcification by multislice computed tomography may contribute to estimation of the extent of atherosclerosis, to diagnosis of CVD in asymptomatic subjects and to assessment of CVD risk. The role of these methods in population screening programmes has not been established.

5. **Intima-media thickness (IMT) of carotid arteries** reflects progression of the atherosclerotic process and may be helpful in prediction of cardiovascular events in asymptomatic patients at intermediate CVD risk. IMT ranging from 0.9 to 1.5 mm is classified as intima-media complex thickening while IMT >1.5 mm is classified as an atherosclerotic plaque.

6. **Coronary calcium score (CS)** equal to zero (CS=0) indicates low risk of cardiovascular events in asymptomatic subjects while in patients with symptoms of ischaemic heart disease it allows the presence of significant coronary artery stenosis to be excluded with high probability.

7. **Heart rate** – lower heart rate is associated with lower CVD risk. Physically active subjects have lower heart rate, and an appropriate level of physical activity is one of the main recommendations in primary and secondary prevention of CVD. An undoubted indication for pharmacological intervention is clinically significant elevated heart rate. However, it is not recommended to lower the heart rate by pharmacological means in order to decrease CVD risk in primary prevention.

8. **Influenza vaccination** – decreases the risk of acute cardiovascular events in patients with established cardiovascular disease. These subjects may benefit from vaccination unless they have a contraindication to receiving the vaccine. Vaccination with intramuscularly administered vaccine should be prescribed annually, optimally before the winter peak in influenza activity.

9. **Assessment of genetic predisposition to cardiovascular diseases** on the basis of family history is required in primary prevention. Premature CVD in first degree (parents, siblings, children) male relatives <55 years and female relatives <65 years is associated with at least twofold increase in CVD risk. The presence of CVD in other relatives has lower significance.

Genetic studies should be prescribed only in patients suspected of rare monogenic diseases, especially familiar hypercholesterolaemia.

10. **Air pollution**, such as a high concentration of small diameter particles <2.5 µm, is associated with increased CVD risk. Air quality monitoring and restrictions on emissions of exhaust fumes from industry should be part of a population strategy in prevention of CVD.

Currently, no efficient methods that could be useful in individual counselling on air pollution in clinical practice are available.

References

1. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004; 364: 937-52.
2. Ridker PM, Libby P. Risk factors for atherothrombotic disease. In: Zipes DP, Libby P, Bonow RO, Braunwald E. Braunwald's Heart Disease. Elsevier 7th Ed. Philadelphia 2005.
3. European guidelines on cardiovascular disease prevention in clinical practice. *Eur J Cardiovasc Prev Rehab* 2003; 10 (Suppl.1): S1-S78.

The Polish version of the guidelines as well as the introductory article and comments from specialists and experts can be read in the seventh issue of Forum Profilaktyki and on the website www.pfp.edu.pl. Authors of these articles are as follows:
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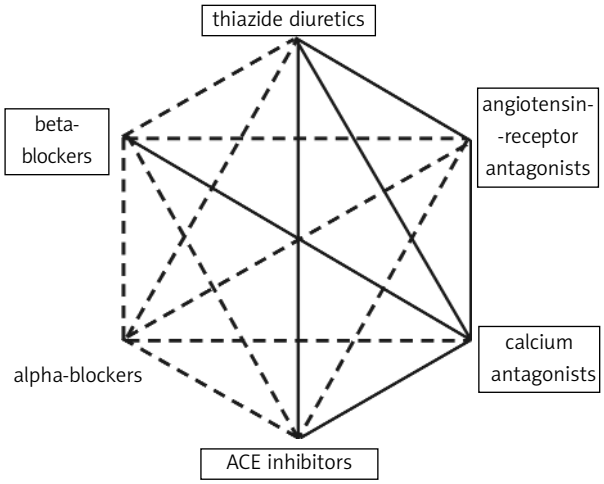
Errata. We wrześniowym numerze *Kardiologii Polskiej* w tekście *Polish Forum for Prevention Guidelines on Arterial Hypertension* Rycina 2. (strona 1139) została wydrukowana z jednym błędem – poniżej wersja poprawiona.



The preferred combinations in the general hypertensive population are represented as thick lines.
The frames indicate classes of agents proven to be beneficial in controlled intervention trials.

Figure 2. Possible combinations between some classes of antihypertensive drugs