SECONDARY PREVENTION OF CARDIOVASCULAR DISEASES: FROM INITIAL FINDINGS TO THE IMPLEMENTATION OF INDIVIDUAL THERAPEUTIC MEASURES

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Abstract

Patients who have survived an acute myocardial infarction, as well as those with atherosclerotic cardiovascular disease, established or unequivocally confirmed by imaging techniques, represent a very high-risk group. This group of patients requires more aggressive treatment of risk factors, regular controls, and monitoring of the effect of therapy. The article aimed to point out the historical importance of risk factors and modern models for assessing residual risk by reviewing the literature. Recognizing the residual risk provides orientation and motivation for more aggressive implementation of secondary preventive therapy on an individual level in daily work with patients and the possibility of reaching the target values recommended by European guidelines.

Keywords: established atherosclerotic cardiovascular disease, secondary prevention, residual risk

Introduction

Cardiovascular diseases, especially coronary heart disease, are the leading cause of death both locally and globally, and they are the most common reason for emergency hospitalization and urgent treatment to prevent fatal outcomes¹⁻³.

In clinical terms, coronary artery disease is not a homogeneous clinical entity. It encompasses a spectrum of acute and chronic coronary syndromes and a range of subtypes of clinical presentations. These presentations can occur not only typically but also atypically, with varying levels of risk and complications, often with unpredictable course and prognosis, including sudden cardiac death⁴⁻⁶.

Acute Myocardial Infarction (AMI) is now promptly recognized and effectively treated, thanks to the use of sophisticated diagnostic methods and laboratory tests, especially with the implementation of (primary) percutaneous coronary interventions, significantly reducing mortality. However, despite this, these patients are at high risk for recurrent major adverse cardiovascular events (MACE) after the index event⁷⁻⁸.

Basic principles of secondary prevention

The European Society of Cardiology - European Association of Preventive Cardiology⁴ in its latest guidelines identifies a high-risk group of patients. This group includes all patients with established atherosclerotic disease - acute coronary syndrome, coronary revascularization, other arterial revascularization procedures, cerebrovascular accident or transient ischemic attack (TIA), aortic aneurysm, and peripheral arterial disease. Additionally, the group includes patients with unequivocally confirmed atherosclerosis (significant plaque on coronary angiography or carotid ultrasound examination). The guidelines⁴ provide further defined therapeutic measures and goals in secondary prevention. Emphasis is placed on the necessity of further identifying patients with residual cardiovascular risk to implement individual strategies in secondary prevention.

The basic principles of secondary prevention are: promoting healthy lifestyle habits (physical activity, healthy diet, and smoking cessation), achieving recommended target values for blood pressure and LDL cholesterol, and using antiplatelet therapy. After implementing preventive measures (defined as the first step⁹), individual assessment of residual risk, life risk, presence of comorbidities, and assessment of the benefits of the applied therapy is recommended (in the second step⁹). Patient education is necessary. The decision is made jointly, respecting personal preferences (Scheme 1).

This group of patients certainly requires more aggressive management of risk factors, regular monitoring and follow-up of treatment effects, as well as calculating individual, or personalized residual risk to further optimize therapy and reduce risk.
Traditional risk factors: The Seven Countries Study and the Framingham Study

The Seven Countries study was the first epidemiological study to investigate the impact of diet and physical activity on the development of cardiovascular diseases.

Keys and colleagues observed significant diversity in dietary patterns and saturated fat intake across 15 different cohorts of patients from seven countries (former Yugoslavia was included with two cohorts: Croatia and Serbia - Zrenjanin, Mala Krsna, and Belgrade). There was a notable difference in cholesterol levels and the incidence of coronary heart disease among the population, both in the five-year and ten-year follow-up periods. This association was confirmed in the twenty-five-year and fifty-year mortality follow-up, leading to the formulation of the Mediterranean Adequacy Index (MAI)\(^9\). The MAI is calculated by dividing the sum of the percentages of energy from typical Mediterranean diet food groups recommended for a healthy diet (such as grains, legumes, vegetables, fresh fruits, nuts, fresh fish, wine, and olive oil) by the sum of energy from less typical food items, the consumption of which is not recommended or limited (such as milk, cheese, meat, eggs, animal fats, margarine, pastries, sugar, sweets, and sweetened beverages). High MAI values were associated with higher mortality rates after 25 years and 50 years (R = -0.84 and R = -0.91, respectively, and R = -0.62 after adjustment for socioeconomic status).

Recognizing its importance, physical activity was included in the content of the first cardiovascular rehabilitation programs in 1968, according to the recommendations of the World Health Organization. Today, there is intensive research on the optimal and therapeutic prescription of physical activity through programs specially designed for secondary prevention - cardiac rehabilitation based on physical activity, which is an integral part of the treatment of these patients\(^11-13\).

The initial results of the leading American study, which celebrated its 75th-anniversary last year, have indicated the existence of factors influencing an increased risk in patients who have experienced AMI if secondary prevention measures are inadequately implemented.

The Framingham Study\(^16\) began at a time when little was known about coronary heart disease and the risk factors leading to its development. Initiated in 1948 in Framingham, a town of 28,000 residents near Boston University, it was selected to conduct one of the largest epidemiological studies on cardiovascular diseases\(^16\).

At first, the study included 5,209 healthy individuals. The original aim was to identify common factors or characteristics for the development of cardiovascular diseases over a twenty years. The initial results\(^16\) (1961) indicated that there were risk factors such as gender, age, elevated blood pressure, cholesterol, obesity, and left ventricular hypertrophy (assessed by electrocardiogram) that contribute to the development of coronary heart disease\(^14\). Soon, other factors were recognized, such as smoking and physical inactivity. The first risk prediction model was formulated in 1967. In the early 1970s, the study was extended, and the examined group was expanded to include a second generation (descendants) of individuals initially included in the study. A third generation of relatives was included in 2002. The Framingham Study thus became a multigenerational study analyzing familial, genetic patterns for cardiovascular and other diseases. In the 1990s, two additional independent cohorts were added to better understand differences in risk profiles associated with racial and ethnic characteristics.

The importance of the Framingham study

The impressive results of the research established the concept of risk factors, enabling an understanding of their impact on the onset of initial manifestations of coronary artery disease, better recognition of subclinical forms, and the physiological profile leading to the development of coronary artery disease (with the help of echocardiography, ambulatory electrocardiogram monitoring, stress tests, biomarkers, multidetector computed tomography of the heart, cardiac magnetic resonance imaging, serial vascular tonometry, and accelerometry), paving the way for further research. Additionally, they contributed to a better understanding of risk factors for heart failure\(^17\) and atrial fibrillation\(^18\).

By detailed formulation of risk factors and their clinical parameters, the findings have been implemented into models for individual assessment of ten-year and thirty-year risk for cardiovascular disease (CVD).

However, mortality in the first year after AMI was high. One in five patients had a fatal outcome, and in the next five years of follow-up, an additional 23% experienced a fatal outcome. Women had a worse prognosis\(^19\). The prognosis of patients was unsatisfactory, so it was not surprising that this subgroup of patients became the focus of research. At that time, mortality in the acute phase of AMI was at least 33%, and it was significantly reduced by establishing

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Scheme 1. Cardiovascular Risk and Risk Factors in Patients with Established Atherosclerotic Cardiovascular Disease\(^a\)

Legend: SBP - Systolic Blood Pressure; LDL - Low Density lipoprotein; DAPT - Dual Antiplatelet Therapy; DPI - Dual Pathway Inhibition.
coronary care units and introducing fibrinolytic therapy, beta-blockers, angiotensin-converting enzyme inhibitors, and anticoagulants. The development of sophisticated diagnostic and therapeutic methods such as coronary angiography, coronary bypass surgery, hemodynamic monitoring, and percutaneous coronary angioplasty also significantly contributed to the reduction in mortality21.

In the chronic phase, high cholesterol levels after recovery from AMI were associated with long-term risk of recurrent myocardial infarction, death from coronary heart disease, and all-cause mortality, necessitating further investigation and appropriate therapy22.

Residual cardiovascular risk

According to one of today’s largest registries, the Swedish registry - SWEDHEART, the risk of recurrent events in over 108,000 patients with AMI was 20% in the first year after the index event, and one in five patients who were stable within the first year had a new event during the three-year follow-up23.

According to data from the GRACE registry (Global Registry of Acute Coronary Events), which included 3,721 patients with Acute Coronary Syndrome (ACS), cardiovascular mortality over a five-year follow-up period was 13%, and the incidence of recurrent myocardial infarction was 9.3%24. Results from the REACH (Reduction of Atherothrombosis for Continued Health) registry emphasized the significance of clinical predictors in the occurrence of future coronary events, highlighting the role of atherosclerosis pathophysiological mechanisms and the biological characteristics of this chronic disease.

The results of assessing cardiovascular risk leading to future events through the prism of pathophysiological mechanisms (metabolic, inflammatory, thrombotic) that contribute to the further progression of atherosclerosis have been incorporated into a strategy for more effective implementation of secondary prevention measures.

Residual metabolic and inflammatory risk

Lowering LDL cholesterol levels is one of the most important tasks in prevention. In secondary prevention25,26, the target LDL cholesterol values are ≤ 1.4 mmol/L, with a reduction of ≥ 50% compared to baseline values (Scheme 1). In patients with established cardiovascular disease who experience recurrent cardiovascular events within two years, lower target LDL values < 1.0 mmol/L may be considered. To achieve target LDL cholesterol levels, among other therapeutic options, statins are recommended. If target values are not achieved with statins, ezetimibe may be added to the therapy, and if success is still lacking, PCSK-9 and/or inclisiran may be considered. In acute coronary syndrome (ACS), high-potency statins at high doses are recommended. In secondary prevention, the dose and choice of medications are adjusted based on LDL values during follow-up, typically after 4-6 weeks, along with lifestyle modifications27. However, only a small percentage of patients reach target LDL cholesterol levels, both worldwide and in our country27,28.

Hypertriglyceridemia is associated with cardiovascular diseases29. Patients with severe primary hypertriglyceridemia should be referred to specialized centers. If triglyceride levels are moderately elevated, > 2.3 mmol/L, the European Society of Cardiology recommends statin therapy for patients at high risk (Class I, Level of Evidence A). If LDL target levels are achieved but triglyceride levels are > 2.3 mmol/L, the addition of fibrates is recommended (Class IIb, Level of Evidence B). Omega-3 ethyl esters at a dose of 2-4 g per day may also be added to statin therapy (Class IIb, Level of Evidence B)30.

Levels of lipoprotein(a), genetically determined LDL containing cholesterol, triglycerides, and apolipoprotein(a), are associated with the development of atherosclerotic cardiovascular disease31 and are determined once during a person’s lifetime. Clinical studies are currently underway to investigate new therapeutic possibilities.

Diabetes is an independent risk factor for CVD32,33. When poorly controlled, diabetes contributes to increased residual cardiovascular risk. The ESC (European Society of Cardiology)34 recommends monitoring all risk factors, controlling blood pressure with target values of 130/80 mmHg, and achieving LDL-C levels < 1.4 mmol/L. To reduce major adverse cardiovascular events (MACE), SGLT2 inhibitors (Sodium-Glucoseco-Transport 2) and GLP1 agonists (Glucagon-like Peptide-1 receptor) are recommended in therapy35.

In secondary prevention, the therapeutic goal is to achieve optimal blood pressure values (Scheme 1) with the proper selection of medications whose effects have been investigated in large clinical studies. Renin-angiotensin-aldosterone system blockers are the first-choice drugs in secondary prevention and are preferred in patients post-AMI, with heart failure, as well as with diabetes in mono or combination therapy (with calcium antagonists or diuretics). Beta-blockers are indicated in patients who have survived AMI and have an ejection fraction < 40%. Among this group, highly selective long-acting beta-blockers such as bisoprolol and nebivolol stand out, although beta-blockers with lower selectivity also have their place. Mineralocorticoid receptor antagonists, in addition to their use in the therapy of patients with concomitant heart failure, also play a role in the treatment of resistant hypertension36,37.

Undoubtedly, hsCRP (High-sensitivity C-reactive protein) is one of the most investigated markers of inflammation in the development and progression of atherosclerotic disease. Statins, with their pleiotropic effects, reduce CRP levels with a significant reduction in risk in populations that have achieved target LDL and hsCRP < 2 mg/L38. There is evidence that anti-inflammatory drugs, such as colchicine at a dose of
0.5 mg, can reduce cardiovascular events in individuals with poor risk factor control or recurrent events despite optimal therapy.

**Residual thrombotic risk**

Acetylsalicylic acid is indicated for all patients with significant coronary artery disease for lifelong use, in the absence of contraindications, at doses of 75-100 mg per day. Dual antiplatelet therapy (aspirin + potent P2Y12 receptor inhibitor, such as ticagrelor or prasugrel) is an essential component of optimal medication therapy within the first year of acute coronary syndrome in the absence of contraindications. In specific clinical cases (assessment of ischemic/thrombotic risk and bleeding risk, presence of comorbidities such as atrial fibrillation requiring oral anticoagulant therapy), antiplatelet therapy may be shortened (<12 months), extended (>12 months), or modified4,4.

**Do models for estimating the residual risks contribute to better clinical practice?**

To define individual risk more closely within a universally defined group of patients with very high cardiovascular risk, several risk assessment models have been formulated. These models are based on easily “measurable” clinical characteristics of patients. Identifying patients with high and very high risk provides clinical guidance for the necessity of implementing more intensive treatment and interventions within a clearly defined period of follow-up.

The EUROASPIRE (European Action on Secondary Prevention through Intervention to Reduce Events) initiative on secondary prevention began in the mid-1990s and has since been conducted in five different studies. The results have been incorporated into numerous clinical guidelines. They have highlighted the high prevalence of smoking, diabetes, obesity, and central obesity in the European population3,3. Despite numerous therapeutic possibilities, target lipid and blood pressure levels are not being achieved. For this reason, EUROASPIRE IV (78 centers from 24 European countries) and V cohorts of patients with coronary heart disease from 27 European countries were integrated to develop a risk assessment model for patients younger than 75 years. A prospective study included 12,484 patients followed for approximately 1.7 years. The primary outcome - fatal cardiovascular disease or recurrent hospitalization due to non-fatal myocardial infarction, stroke, heart failure, coronary artery bypass grafting (CABG), or percutaneous coronary intervention (PCI) - was recorded in 1,424 patients. The model was validated in 20,148 patients after AMI from the SWED-HEART registry. A calculator has been developed to estimate the risk within the first and second year following the index event3,34(An index event), and Serbia is included in the model.

The SMART (Secondary Manifestation of ARterial disease) model estimates the individual residual risk for recurrent myocardial infarction, stroke, or vascular death (Table 2). The study included a cohort of patients in Utrecht, and the results obtained were validated in several external clinical studies. However, the model included patients enrolled before 2010 who were followed for 4.7 years, so it could not reliably be applied to assess the ten-year risk. Additionally, it did not include parameters related to regional differences in CVD incidence, as well as other diseases that may lead to fatal outcomes unrelated to CVD.

The SMART 2 model was developed by enhancing the mentioned parameters and included 377,399 patients with coronary, cerebral, and peripheral atherosclerosis aged 40 to 80 years, with 64,513 new events3,3. It is formulated in such a way that using an online calculator, the residual risk and the possibility of its reduction through the optimization of individual parameters can be calculated. It is expected to be available for clinical use soon.

The SMART REACH model indeed estimates both the ten-year residual and lifetime risk23,39. The model has been developed and validated in the prospective SMART and REACH cohorts: 14.259 (REACH Western Europe), 19.170 (REACH, North America), and 6.959 (SMART, Netherlands)
patients with cardiovascular diseases. It can contribute to clinical decision-making regarding appropriate therapeutic strategies to reduce risk. Clinical parameters shown in Table 3 are required for online calculation. It supports addressing clinical dilemmas regarding therapy intensity and may be significant in better implementing secondary prevention measures. It effectively defines an individual ten-year life risk and its reduction. The Model requires further optimization and reliability testing in patients with peripheral arterial disease.

Table 3. Clinical parameters necessary for calculating residual and lifetime risk using the SMART REACH model8, 37-39

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geographical region (Western Europe, Netherlands, North America, other)</td>
<td></td>
</tr>
<tr>
<td>Time since cardiovascular event (number of years)</td>
<td></td>
</tr>
<tr>
<td>Type of cardiovascular event (coronary, peripheral, or cerebrovascular arterial disease)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus (yes/no)</td>
<td></td>
</tr>
<tr>
<td>Heart failure (yes/no)</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation (yes/no)</td>
<td></td>
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<tr>
<td>Value of systolic blood pressure</td>
<td></td>
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<tr>
<td>Creatinine</td>
<td></td>
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<tr>
<td>Lipid profile: Total cholesterol, LDL cholesterol</td>
<td></td>
</tr>
<tr>
<td>Statin (yes, no, which, and in what dose)</td>
<td></td>
</tr>
<tr>
<td>Ezetimib (yes/no)</td>
<td></td>
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<tr>
<td>PCSK9 (yes/no)</td>
<td></td>
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<tr>
<td>Antiplatlet/monotherapy: acetylsalicylic acid or equivalent/acetylsalicylic acid alone, or acetylsalicylic acid + low-dose DOAC</td>
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</table>

Legend: DOAC: Direct Oral Anti Coagulant.

Conclusion

Our understanding of a comprehensive approach to patients with clinically proven coronary artery disease according to their clinical characteristics is constantly evolving. Simultaneously, modern therapeutic models and tools are being developed to help in their application. Undoubtedly, defining residual risk will contribute to a better understanding of personal preferences in achieving desired and clearly defined therapeutic goals and adequate secondary prevention to prolong life and improve the quality of life for these patients.

Literature


