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# Polish Forum for Prevention of Cardiovascular Diseases Guidelines on prophylactic pharmacotherapy

## Wytyczne Polskiego Forum Profilaktyki Chorób Układu Krążenia dotyczące farmakoterapii prewencyjnej

Piotr Podolec, Grzegorz Kopeć, Anetta Undas, Andrzej Pająk, Maciej Godycki-Ćwirko, Tomasz Zdrojewski, Piotr Jankowski, Wojciech Drygas, Andrzej Rynkiewicz, Ryszard Piotrowicz, Danuta Czarnecka, Marek Naruszewicz, Grzegorz Opala, Jerzy Stańczyk, Elżbieta Kozek, Adam Windak, Waldemar Banasiak, Tomasz Guzik

Polish Forum for Prevention of Cardiovascular Diseases Task Force on Guidelines

**1. Prophylactic pharmacotherapy** is, second only to a healthy lifestyle, the primary method of preventing cardiovascular disease (CVD). Its introduction explains about 20% reduction in mortality from coronary heart disease that have occurred in developed countries (changes in risk factors — about 50%, the introduction of invasive procedures — about 10%) [1].

**2. Prophylactic pharmacotherapy includes** the use of drugs which decrease the risk of developing CVD, and death from CVD, regardless of the impact on major CVD risk factors. It includes drugs:

— that improve survival (reduce the risk of death from any cause): antiplatelet drugs (aspirin and thienopyridine), statins (discussed in the PFP guidelines on dyslipidaemia) [2]; beta-blockers, angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), omega-3 fatty acids (discussed in the PFP guidelines on dyslipidaemia) [2];

— that reduce the risk of CVD events with no effect on overall survival: influenza vaccination (discussed in the 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 CVD) [3], ivabradine [3].

**3. Acetylosalicylic acid (ASA).** In primary prevention, ASA reduces the risk of myocardial infarction (MI) in men by 32% and the risk of stroke in women by 17%, although it does not affect the risk of death. Its chronic use increases the risk of bleeding (including life-threatening gastrointestinal or intracranial bleeding).

It is recommended that patients be encouraged to use aspirin (75 mg once a day) only if the potential benefit from its use is greater than the risk of bleeding. This usually involves people who have a ten year risk of death from CVD > 10% as assessed by SCORE charts and adequate control of hypertension (< 140/90 mm Hg), and subjects with diabetes type 1, or type 2 > 50 years of age (men) and > 60 years of age (women), coexisting with at least one additional CVD risk factor, i.e.: positive family history, smoking, hypertension, hypercholesterolaemia or albuminuria.

It is recommended that aspirin not be used as primary prevention in men < 45 years or women < 55 years.

In the secondary prevention of CVD in patients with recent MI or ischaemic stroke, unstable or stable angina, peripheral artery disease, or transient ischaemic attack, and in patients with atrial fibrillation, the use of aspirin reduces the risk of death by 15%.

Aspirin is recommended as secondary prevention of CVD, unless there are contraindications:

— in a single loading dose of 150–325 mg in acute coronary syndromes and ischaemic stroke;

— indefinitely at a dose of 75–100 mg once a day in patients with diagnosed CVD; in cases of hypersensitivity to aspirin, clopidogrel is recommended at a dose of 75 mg once a day.

Contraindications: hypersensitivity or intolerance to the drug and active bleeding [4–7].

**4. Clopidogrel.** In acute MI, the addition of clopidogrel to aspirin throughout hospitalisation reduces the risk of death by 7%. Adding clopidogrel to aspirin for 3–12 months after

**Address for correspondence:**
prof. Piotr Podolec, MD, PhD, Department of Cardiac and Vascular Diseases, Institute of Cardiology, *Collegium Medicum*, Jagiellonian University, John Paul II Hospital, ul. Prądnicka 80, 31–202 Kraków, Poland, tel: +48 12 614 33 99, fax: +48 12 614 34 23, e-mail: ppodolec@interia.pl

acute coronary syndrome (ACS) without ST segment elevation reduces the risk of CVD events in 12 months by 14%.

It is recommended that dual antiplatelet therapy be prescribed: clopidogrel in combination with aspirin in patients:
— with ACS in a loading dose;
— after an ACS for 12 months at a dose of 75 mg once a day;
— with stable coronary artery disease treated with percutaneous coronary intervention with implantation of a bare metal stent (for a month) or a drug-eluting stent (for 6––12 months) at a dose of 75 mg once a day.

Contraindications to the use of clopidogrel are: hypersensitivity to the drug, severe liver damage, active bleeding, pregnancy and lactation, recent stroke [8–12].

**5. Beta-blockers**, when used chronically after MI, reduce the risk of death by 23%. Bisoprolol, carvedilol and metoprolol (succinate) reduce the risk of death in patients with symptomatic heart failure (HF) and low left ventricular ejection fraction (LVEF < 35–45%) by 30%. Nebivolol reduces the risk of death or hospitalisation in patients with HF > 70 years of age by 14%. Beta-blockers used in combination with ACEI reduce the risk of death in asymptomatic patients with reduced LVEF by 25–30%.

It is recommended that beta-blockers be used indefinitely to prevent CVD events in patients:
— after MI; oral therapy is preferred and should be initiated after stabilisation of the haemodynamic status;
— with reduced LVEF < 40% in functional class I–IV [bisoprolol, carvedilol, metoprolol (succinate), nebivolol].

Beta-blockers are also used as antiarrhythmic, antihypertensive and antianginal drugs.

Contraindications: poorly controlled asthma and atrioventricular block of second or third degree, sick sinus syndrome, sinus bradycardia < 50/min. In the case of contraindications to beta-blockers in patients after MI without evidence of HF, verapamil should be considered as an alternative (it reduces the risk of death by 36%) [13–27].

**6. ACE inhibitors** reduce the risk of death in patients with coronary artery disease without HF by 13%, for patients with HF of different etiologies by 16–27%, and for patients with asymptomatic left ventricular dysfunction of different etiologies by 14–19%.

ACEIs are recommended to reduce the risk of CVD in patients:
— with reduced LVEF ≤ 40%, irrespective of the presence of the clinical symptoms of HF;
— with ischaemic heart disease and diabetes or hypertension;
— with diabetes and albuminuria or hypertension;
— and in the treatment of hypertension.

Their use should be considered also in patients with diagnosed stable coronary artery disease and after MI.

ACEIs are not homogeneous drugs. When choosing a specific medication, one should consider the results of clinical studies and the lack of a class effect, especially in the prevention of vascular complications.

Contraindications: a history of angioedema, bilateral renal artery stenosis or stenosis of a single renal artery, pregnancy, cardiomyopathy with left ventricle outflow tract obstruction, severe aortic stenosis, serum potassium > 5 mmoL/L (relative), serum creatinine > 220 mmoL/L (2.5 mg/dL) (relative) [28–33].

**7. Angiotensin receptor blockers.** Adding ARBs to ACEIs in patients with HF and reduced LVEF reduces the risk of death from CVD by 16% and hospitalisations for HF by 17% to 34%, but does not affect the overall risk of death. In patients with HF and reduced ejection fraction who cannot tolerate an ACEI, the use of ARBs compared to a placebo reduces the risk of death from CVD by 20% and hospitalisation for HF by 39%. In patients after MI with HF or reduced ejection fraction, ARBs affect the risk of death similarly to ACEIs.

ARBs are recommended to improve prognosis in patients with hypertension, in patients after MI or HF who do not tolerate ACEI, and together with ACEI in patients with LVEF < 40% and with persistent symptoms of HF despite optimal medical treatment with ACEIs and beta-blockers, provided no aldosterone antagonist is used.

Contraindications are the same as for ACEI, except for angioedema. An ARB should not be added to patients receiving an ACEI and an aldosterone antagonist [34–38].

**8. Aldosterone antagonists** reduce the risk of death in patients with LVEF ≤ 35% and functional class III or IV treated with an ACEI and a loop diuretic by 30% (spironolactone) and in patients after MI with LVEF ≤ 40%, and symptoms of HF or diabetes treated with ACEI or ARB, diuretics and beta-blocker by 15% (eplerenone).

They are recommended to improve prognosis in patients with HF functional class III or IV, LVEF ≤ 35%, who are optimally treated with beta-blockers and ACEIs or ARBs.

Contraindications: blood potassium > 5.0 mmoL/L, serum creatinine > 220 mmoL/L, the use of a combination of ACEI and ARB or the combination of potassium-sparing diuretic with potassium supplements [39, 40].

**9. Pharmacotherapy** plays an important role in modifying risk factors for CVD such as dyslipidaemia, hypertension and diabetes, and this modification significantly reduces the risk of CVD.

**10. Some drugs used in patients with CVD** do not affect the risk of CVD, but improve quality of life. This group includes for example nitrates used in stable coronary artery disease to abolish anginal symptoms, as well as digoxin or diuretics used in HF.

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## *References*

1. Ford ES, Ajani UA, Croft JB et al. Explaining the decrease in U.S. deaths from coronary disease, 1980–2000. N Engl J Med, 2007; 356: 2388–2398.
2. Cybulska B, Szostak WB, Podolec P et al. Polish Forum for Prevention Guidelines on dyslipidemia. Kardiol Pol, 2008; 66: 1239–1242.
3. Undas A, Podolec P, Kopeć G et al. 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. Kardiol Pol, 2007; 65: 1396–1398.

4. US Preventive Services Task Force. Aspirin for the prevention of cardiovascular disease: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med, 2009; 17: 396–404.
5. Graham I, Atar D, Borch-Johnsen K et al. European guidelines on cardiovascular disease prevention in clinical practice: executive summary: Fourth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (Constituted by representatives of nine societies and by invited experts). Eur Heart J, 2007; 28: 2375–2414.
6. Standards of Medical Care in Diabetes: 2010. Diabetes Care, 2010; 33 (suppl. 1): S11–S61.
7. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ, 2002; 12: 71–86.
8. Bassand JP, Hamm CW, Ardissino D et al. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. Eur Heart J, 2007; 28: 1598–1660.
9. Van de Werf F, Bax J, Betriu A et al. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: the Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology. Eur Heart J, 2008; 29: 2909–2945.
10. European Association for Percutaneous Cardiovascular Interventions. ESC Committee for Practice Guidelines. Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J, 2010; 31: 2501–2555.
11. European Stroke Organisation (ESO) Executive Committee; ESO Writing Committee. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. Cerebrovasc Dis, 2008; 25: 457–507.
12. Yusuf S, Zhao F, Mehta SR et al. Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med, 2001; 345: 494–502.
13. Chen ZM, Jiang LX, Chen YP et al. COMMIT (ClOpidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet, 2005; 366: 1607–1621.
14. Freemantle N, Cleland J, Young P et al. Beta-blockade after myocardial infarction: systematic review and meta regression analysis. BMJ, 1999; 318: 1730–1737.
15. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II). A randomised trial. Lancet, 1999; 353: 9–13.
16. Australia/New Zealand Heart Failure Research Collaborative Group. Randomised, placebo-controlled trial of carvedilol in patients with congestive heart failure due to ischaemic heart disease. Lancet, 1997; 349: 375–380.
17. Packer M, Bristow MR, Cohn JN et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. N Engl J Med, 1996; 334: 1349–1355.
18. Packer M, Fowler MB, Roecker EB et al. Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Study Group. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. Circulation, 2002; 22: 2194–2199.
19. Effect of metoprolol CR/XL in chronic heart failure. Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet, 1999; 353: 2001–2007.
20. Flather MD, Shibata MC, Coats AJ et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). Eur Heart J, 2005; 26: 215–225.
21. Exner DV, Dries DL, Waclawiw MA, Shelton B, Domanski MJ. Beta-adrenergic blocking agent use and mortality in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: a post hoc analysis of the Studies of Left Ventricular Dysfunction. J Am Coll Cardiol, 1999; 33: 916–923.
22. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. Lancet, 2001; 357: 1385–1390.
23. Vantrimpont P, Rouleau JL, Wun CC et al. Additive beneficial effects of beta-blockers to angiotensin-converting enzyme inhibitors in the Survival and Ventricular Enlargement (SAVE) Study. SAVE Investigators. J Am Coll Cardiol, 1997; 29: 229–236.
24. Doughty RN, Whalley GA, Walsh HA, Gamble GD, López-Sendón J, Sharpe N. Effects of carvedilol on left ventricular remodeling after acute myocardial infarction: the CAPRICORN Echo Substudy. Circulation, 2004; 109: 201–206.
25. Remme WJ, Riegger G, Hildebrandt P et al. The benefits of early combination treatment of carvedilol and an ACE-inhibitor in mild heart failure and left ventricular systolic dysfunction. The carvedilol and ACE-inhibitor remodelling mild heart failure evaluation trial (CARMEN). Cardiovasc Drugs Ther, 2004; 18: 57–66.
26. Colucci WS, Kolias TJ, Adams KF et al. Metoprolol reverses left ventricular remodeling in patients with asymptomatic systolic dysfunction: the REversal of VEntricular Remodeling with Toprol-XL (REVERT) trial. Circulation, 2007; 116: 49–56.
27. Task Force for Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of European Society of Cardiology. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008. Eur Heart J, 2008; 29: 2388–2442.
28. Al-Mallah MH, Tleyjeh IM, Abdel-Latif AA, Weaver WD. Angiotensin-converting enzyme inhibitors in coronary artery disease and preserved left ventricular systolic function: a systematic review and meta-analysis of randomized controlled trials. J Am Coll Cardiol, 2006; 47: 1576–1583.
29. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med, 1987; 316: 1429–1435.
30. Jong P, Yusuf S, Rousseau MF, Ahn SA, Bangdiwala SI. Effect of enalapril on 12-year survival and life expectancy in patients with left ventricular systolic dysfunction: a follow-up study. Lancet, 2003; 361: 1843–1848.
31. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. Lancet, 1993; 342: 821–828.
32. Køber L, Torp-Pedersen C, Carlsen JE et al. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (TRACE) Study Group. N Engl J Med, 1995; 333: 1670–1676.
33. Pfeffer MA, Braunwald E, Moyé LA et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. N Engl J Med, 1992; 327: 669–677.
34. McMurray JJ, Ostergren J, Swedberg K et al. CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. Lancet, 2003; 362: 767–771.
35. Krum H, Carson P, Farsang C et al. Effect of valsartan added to background ACE inhibitor therapy in patients with heart failure: results from Val-HeFT. Eur J Heart Fail, 2004; 6: 937–945.
36. Granger CB, McMurray JJ, Yusuf S et al. CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. Lancet, 2003; 362: 772–776.
37. Pfeffer MA, McMurray JJ, Velazquez EJ et al. Valsartan in Acute Myocardial Infarction Trial Investigators. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med, 2003; 349: 1893–1906.
38. Dickstein K, Kjekshus J; OPTIMAAL Steering Committee of the OPTIMAAL Study Group. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan. Lancet, 2002; 360: 752–760.
39. Pitt B, Zannad F, Remme WJ et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med, 1999; 341: 709–717.
40. Pitt B, Remme W, Zannad F et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. N Engl J Med, 2003; 348: 1309–1321.