

Polish Forum for Prevention Guidelines on Prophylactic Pharmacotherapy: update 2017

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Piotr Podolec¹, Krzysztof J. Filipiak², Anetta Undas³, Andrzej Pająk⁴, Maciek Godycki-Ćwirko⁵, Wojciech Drygas⁶, Tomasz Zdrojewski⁷, Piotr Jankowski⁸, Jakub Podolec⁹, Monika Komar¹, Agnieszka Sarnicka¹, Elżbieta Kozek¹⁰, Danuta Czarna⁸, Maciej Małecki¹⁰, Grażyna Nowicka¹¹, Anna Członkowska¹², Maciej Niewada¹³, Jerzy Stańczyk¹⁴, Adam Windak¹⁵, Tomasz Guzik¹⁶, Grzegorz Kopec¹

¹Department of Cardiac and Vascular Diseases, Institute of Cardiology, Jagiellonian University Medical College at John Paul II Hospital, Krakow, Poland

²^{1st} Department of Cardiology, Medical University of Warsaw, Warsaw, Poland

³Institute of Cardiology, Jagiellonian University Medical College, Krakow, Poland

⁴Chair of Epidemiology and Population Studies, Institute of Public Health, Faculty of Health Sciences, Jagiellonian University Medical College, Krakow, Poland

⁵Centre for Family and Community Medicine, Faculty of Health Sciences, Medical University of Lodz, Lodz, Poland

⁶Department of Epidemiology, CVD Prevention, and Health Promotion, Institute of Cardiology, Warsaw, Poland

⁷Department of Preventive Medicine and Medical Education, Medical University in Gdansk, Gdansk, Poland

⁸^{1st} Department of Cardiology, Interventional Electrophysiology and Hypertension, Institute of Cardiology, Jagiellonian University Medical College, Krakow, Poland

⁹Department of Haemodynamics and Angiocardiology, John Paul II Hospital, Institute of Cardiology, Jagiellonian University Medical College, Krakow, Poland

¹⁰Department of Metabolic Diseases, Jagiellonian University Medical College, Krakow, Poland

¹¹Department of Pharmacogenomics, Division of Biochemistry and Clinical Chemistry, Medical University of Warsaw, Warsaw, Poland

¹²^{2nd} Department of Neurology, Institute of Psychiatry and Neurology, Warsaw, Poland

¹³Department of Experimental and Clinical Pharmacology, Medical University of Warsaw, Warsaw, Poland

¹⁴Department of Paediatric Cardiology and Rheumatology, Medical University of Lodz, Lodz, Poland

¹⁵Department of Family Medicine, Jagiellonian University Medical College, Krakow, Poland

¹⁶Department of Internal Diseases and Rural Medicine, Jagiellonian University Medical College, Krakow, Poland

NEW IN 2017: UPDATE OF POLISH FORUM FOR PREVENTION GUIDELINES ON PROPHYLACTIC PHARMACOTHERAPY

1. Acetylsalicylic acid (ASA) not recommended in primary prevention of cardiovascular diseases (CVD)
2. New antiplatelet drugs after acute coronary syndrome (ACS) and percutaneous coronary interventions (PCI)
3. Sacubitril-valsartan for selected patients with heart failure (HF) with reduced ejection fraction (EF)
4. Recommendations on stroke prevention therapy in atrial fibrillation (AF) patients
5. Modified recommendations on combination therapy with oral anticoagulant and antiplatelets in AF patients

1. PROPHYLACTIC PHARMACOTHERAPY

Prophylactic pharmacotherapy is, second only to lifestyle changes, the primary method of prevention of CVD. The reduction, by half, of the mortality from coronary heart disease in Poland between 1991 and 2005 resulted from a reduction of the prevalence of CVD risk factors (54%) and implemented therapies (37%), mainly pharmacological [1].

2. AIMS OF PROPHYLACTIC PHARMACOTHERAPY

Prophylactic pharmacotherapy includes the use of drugs, which, in primary and/or secondary prevention, decrease the risk of developing CVD and death from CVD. It includes drugs:

Address for correspondence:

Piotr Podolec, MD, PhD, Department of Cardiac and Vascular Diseases, Institute of Cardiology, Jagiellonian University Medical College, John Paul II Hospital, Centre for Rare Cardiovascular Diseases in Krakow, ul. Prądnicka 80, 31–202 Kraków, Poland, e-mail: ppodolec@interia.pl

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- **that improve survival** (reduce the risk of death from any cause): antiplatelet drugs, statins (discussed in the PFP guidelines on dyslipidaemia [2]), beta-blockers, angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), aldosterone antagonists (MRA), omega-3 fatty acids, combination of valsartan and sacubitril;
- **that reduce the risk of CVD events with no effect on overall survival**: influenza vaccination, ivabradine [3];
- **that improve the quality of life with no effect on the risk of CVD events**: nitrates, digoxin [4].

3. ACETYLSALICYLIC ACID (ASA)

Indications:

- **primary prevention of CVD** — ASA reduces the risk of myocardial infarction (MI) in men by 32% and the risk of stroke in women by 17%; however, it does not affect the risk of death. Its chronic use increases the risk of bleeding (including life-threatening gastrointestinal or intracranial bleeding). **Therefore, routine use of ASA is not recommended in primary prevention;**
- **secondary prevention of CVD** — in patients with known CVD and in patients with AF, the use of ASA reduces the risk of death by 15%. **ASA is recommended in secondary prevention of CVD, unless there are contraindications.**

Doses:

- in a single loading dose of 150–325 mg in ACS or during PCI in patients not previously treated with ASA, and the loading dose of 160–325 mg in ischaemic stroke (in the case of thrombolytic treatment of stroke, ASA should not be administered on the first day);
- indefinitely at a dose of 75–100 mg once a day in patients with diagnosed CVD, and 50–325 mg once a day in patients after ischaemic stroke; in cases of hypersensitivity to ASA, clopidogrel is recommended at a dose of 75 mg once a day.

Main contraindications to use of ASA: hypersensitivity or intolerance to the drug and active bleeding [5–9].

4. DUAL ANTIPLATELET THERAPY (DAPT)

The most common combinations of antiplatelet drugs are: clopidogrel, ticagrelor or prasugrel in addition to ASA.

In acute MI, the addition of clopidogrel to ASA during hospitalisation reduces the risk of death by 7%. Adding clopidogrel to ASA for 3–12 months after ACS without ST segment elevation reduces the risk of CVD events in 12-month follow-up by 14%. The use of ticagrelor or prasugrel instead of clopidogrel in addition to ASA in patients with MI treated with primary PCI results in an additional reduction in risk of CVD deaths and events.

Recommended dose of antiplatelet drugs (P2Y₁₂ inhibitors):

- clopidogrel — loading dose of 600 mg, maintenance dose of 75 mg once a day;

- prasugrel — loading dose 60 mg, maintenance dose of 10 mg once a day;
- ticagrelor — loading dose 180 mg, maintenance dose of 90 mg twice daily.

- Indications:** Use of DAPT is recommended in patients:
- **with ACS** — in a single loading dose followed by a maintenance dose for 12 months (preferred use of ASA plus ticagrelor or prasugrel; when they are not available or contraindicated — ASA plus clopidogrel);
 - **with stable coronary artery disease (CAD), treated with PCI with stent implantation** — in a single loading dose followed by maintenance dose — for a month after bare metal stent implantation and for six months after drug-eluting stent implantation (routine use of clopidogrel is recommended, in case of stent thrombosis on clopidogrel therapy — ticagrelor or prasugrel is recommended) in addition to ASA;
 - **with ischaemic stroke** — in an acute period only monotherapy with ASA is used; in secondary prevention monotherapy with ASA or clopidogrel is recommended. DAPT increases the risk of intracranial bleeding; therefore, at present DAPT with clopidogrel and ASA is not recommended.

Main contraindications to use of P2Y₁₂ inhibitors: hypersensitivity, severe liver damage, active bleeding, and additionally: for clopidogrel — recent stroke; for prasugrel — previous stroke or transient ischaemic attack; and for ticagrelor — previous intracranial haemorrhage and the parallel use of CYP3A4 inhibitors [6–9].

5. BETA-BLOCKERS

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 HF with reduced EF (HFrEF) 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 ACEIs reduce the risk of death in asymptomatic patients with reduced left ventricular ejection fraction (LVEF) by 25–30%.

Indications: 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 HFrEF in functional class II–IV (bisoprolol, carvedilol, metoprolol [succinate], nebivolol) in combination with ACEIs or ARBs.

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

Main contraindications to use of beta-blockers: hypersensitivity to the drug, poorly controlled asthma, atrioventricular block of second or third degree, sick sinus syndrome, sinus bradycardia < 50/min, cardiogenic shock, decompensated HF (Killip class ≥ III), vasospastic angina, and severe peripheral arterial disease. 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%) [4, 6, 7, 9, 10].

6. ANGIOTENSIN-CONVERTING ENZYME INHIBITORS (ACEIs)

ACEIs reduce the risk of death in patients with CAD without HF by 13%, in patients with HF of different aetiologies by 16–27%, and in patients with asymptomatic left ventricular dysfunction of different aetiologies by 14–19%.

Indications: ACEIs are recommended to reduce the risk of cardiovascular events in patients:

- with HFrEF in functional class II–IV;
- with CAD and coexisting conditions such as HF, diabetes, or hypertension;
- with diabetes and albuminuria or hypertension;
- in the treatment of hypertension.

Their use should be considered also in patients with diagnosed stable CAD 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.

Main contraindications to use of ACEIs: hypersensitivity to the drug, a history of angioedema, bilateral renal artery stenosis or stenosis of a single renal artery, pregnancy and lactation, cardiomyopathy with left ventricular outflow tract obstruction, severe aortic stenosis, serum potassium > 5 mmol/L (relative), serum creatinine > 220 μ mol/L (2.5 mg/dL) (relative) [4, 6, 7, 9, 10].

7. ANGIOTENSIN RECEPTOR BLOCKERS (ARBs)

In patients with HFrEF, who cannot tolerate ACEIs, 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 HFrEF, ARBs affect the risk of death similarly to ACEIs. A combination of valsartan and sacubitril (angiotensin receptor neprilysin inhibitor [ARNI]) reduce the risk of death by 16% and hospitalisation for HF by 21% in patients with HFrEF in comparison to enalapril.

Indications: ARBs are recommended to improve prognosis in patients with hypertension, HFrEF, or after MI, who do not tolerate ACEI. All three drugs that inhibit the renin–angiotensin–aldosterone system (ACEI, ARB, and aldosterone antagonist) should not be given together. ARNI is recommended as a replacement for an ACEI in patients with HFrEF, who remain symptomatic despite optimal treatment with an ACEI, a beta-blocker, and MRA.

Main contraindications to use of ARBs: are the same as for ACEI, except for angioedema. An ARB should not be added in patients receiving an ACEI and an aldosterone antagonist. Combined treatment with an ACEI or ARB and ARNI is contraindicated [4, 9, 10].

Table 1. CHA₂DS₂-VASc score for stroke risk assessment in atrial fibrillation patients [11]

CHA ₂ DS ₂ -VASc risk factor	Points
Congestive heart failure	1
Hypertension	1
Age 75 years or older	2
Diabetes mellitus	1
Previous stroke, transient ischaemic attack, or thromboembolism	2
Vascular disease (previous myocardial infarction, peripheral artery disease)	1
Age 65–74 years	1
Sex category (female)	1

8. ALDOSTERONE ANTAGONISTS (MRAs)

MRAs reduce the risk of death in patients with LVEF \leq 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 \leq 40% and symptoms of HF or diabetes treated with ACEI or ARB, beta-blocker, and diuretics by 15% (eplerenone).

Indications: MRAs are recommended to improve prognosis in patients with HF with LVEF \leq 35% and functional class II–IV, who are optimally treated with beta-blockers and ACEIs or ARBs.

Main contraindications to use of MRAs: hypersensitivity to the drug, blood potassium > 5.0 mmol/L, severe renal impairment — creatinine clearance < 30 mL/min, severe liver dysfunction — Child and Pugh class C, and the use of a combination of ACEI and ARB or the combination of potassium-sparing diuretic with potassium supplements [10].

9. ORAL ANTICOAGULATION — STROKE PREVENTION THERAPY IN AF PATIENTS

Oral anticoagulation (OAC) reduces the risk of stroke in AF by 65%, while antiplatelet drugs only by 20%.

Indications: OAC is recommended in AF patients with a CHA₂DS₂-VASc score of 2 or more for men, and 3 or more for women. OAC should also be considered for men with a CHA₂DS₂-VASc score of 1 and women with a score of 2 (Table 1):

- non-vitamin K antagonist oral anticoagulants (NOACs), i.e. direct thrombin inhibitor (dabigatran) or factor Xa inhibitors (rivaroxaban, apixaban or edoxaban), dose dependent on renal function and the risk of bleeding;
- vitamin K antagonists, i.e. warfarin, acenocumarol in adjusted dose (INR 2.0–3.0).

NOACs are not recommended in patients with mechanical heart valves or moderate-to-severe mitral stenosis.

Antiplatelet therapy is not recommended for stroke prevention in AF patients.

Contraindications: hypersensitivity to the drug, pregnancy, active bleeding, recent intracranial haemorrhage or surgery of the central nervous system or the eye, conditions increasing the risk of major bleeding, and for NOAC additionally severe renal impairment.

Combination therapy with OACs and antiplatelets (ASA and clopidogrel) in AF patients after ACS or PCI (in particular its duration) is dependent on the type of intervention (ACS or elective PCI) and assessment the risk of bleeding (i.e. HASBLED score) compared to the risk of ACS or stent thrombosis [11].

10. PHARMACOTHERAPY OF RISK FACTORS

Prophylactic pharmacotherapy plays an important role in modifying risk factors for CVD such as dyslipidaemia, hypertension, and diabetes, as well as tobacco dependence [2, 12–14].

Conflict of interest: none declared

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