

Rosuvastatin-based combination treatment with acetylsalicylic acid or ezetimibe in the management of patients at high and very high cardiovascular risk. Expert opinion paper of the Polish Lipid Association 2025

Maciej Banach^{1,2,3,4*}, Stanisław Surma^{2,5}, Agata Bielecka-Dąbrowa^{2,6}, Marek Gierlotka⁷, Renata Głowczyńska⁸, Piotr Jankowski^{9,10}, Jacek Józwiak¹¹, Jacek Kubica¹², Witold Streb^{13,14}, Filip M. Szymański¹⁵, Tomasz Tomasiak¹⁶, Robert Gil¹⁷

¹Faculty of Medicine, John Paul II Catholic University of Lublin (KUL), Poland

²Department of Preventive Cardiology and Lipidology, Medical University of Lodz (MUL), Poland

³Ciccarone Center for the Prevention of Cardiovascular Disease, Johns Hopkins University School of Medicine, Baltimore, MD, USA

⁴Liverpool Centre for Cardiovascular Science (LCCS), Liverpool, UK

⁵Department of Internal Medicine and Clinical Pharmacology, Medical University of Silesia, Katowice, Poland

⁶Department of Cardiology and Congenital Diseases of Adults, Polish Mother's Memorial Hospital Research Institute (PMMHRI), Lodz, Poland

⁷Department of Cardiology, Institute of Medical Sciences, University of Opole, Poland

⁸1st Department of Cardiology, Medical University of Warsaw, Poland

⁹Department of Internal Medicine and Geriatric Cardiology, Medical Centre of Postgraduate Education, Warsaw, Poland

¹⁰Department of Epidemiology and Health Promotion, School of Public Health, Centre of Postgraduate Medical Education, Warsaw, Poland

¹¹Department of Family Medicine and Public Health, Institute of Medical Sciences, University of Opole, Poland

¹²Department of Cardiology and Internal Medicine, Nicolaus Copernicus University, Bydgoszcz, Poland

¹³1st Department of Cardiology and Angiology, Silesian Center for Heart Diseases, Zabrze, Poland

¹⁴Department of Cardiology, Congenital Heart Diseases and Electrotherapy, Division of Medical Sciences in Zabrze, Medical University of Silesia, Silesian Center for Heart Diseases, Zabrze, Poland

¹⁵Department of Civilization Diseases, Faculty of Medicine, Collegium Medicum, Cardinal Stefan Wyszyński University, Warsaw, Poland

¹⁶Department of Family Medicine, Jagiellonian University Medical College, Krakow, Poland

¹⁷Department of Cardiology, National Institute of Medicine of the Ministry of the Interior and Administration, Warsaw, Poland

*Corresponding author:

Prof. Maciej Banach, MD, PhD, FNLA, FAHA, FESC
Faculty of Medicine
John Paul II Catholic
University of Lublin (KUL)
Lublin, Poland
E-mail: maciej.banach@kul.pl

Submitted: 10 October 2024; **Accepted:** 7 January 2025

Online publication: 7 January 2025

Arch Med Sci 2025; 21 (1): 1–15

DOI: <https://doi.org/10.5114/aoms/199826>

Copyright © 2025 Termedia & Banach

Abstract

Lipid disorders are the most common risk factor for atherosclerotic cardiovascular disease (ASCVD) in Poland, where it is responsible for up to 200,000 deaths per year, with the number of myocardial infarctions and strokes reaching 80,000 annually and 25% of people dying within 3 years after a myocardial infarction. Despite the availability of effective drugs, the level of control of low-density lipoprotein cholesterol (LDL-C) is low, at only about 20% among high- and very high-risk patients, who often require combination lipid-lowering therapy (LLT) with a potent statin (e.g. rosuvastatin) and ezetimibe. Moreover, in Poland, several million patients require concom-

itant lipid-lowering and antiplatelet (acetylsalicylic acid) therapy based on their risks and indications. Single pill combinations (SPCs) improve adherence to treatment as well as the achievement of therapeutic goals and allow a greater reduction in cardiovascular incidents and mortality. This expert opinion paper, endorsed by the Polish Lipid Association (PoLA), provides practical recommendations for more effective treatment of patients with indications for LLT and antiplatelet therapy using available rosuvastatin-based combination therapies (with ezetimibe or acetylsalicylic acid).

Key words: cardiovascular risk, rosuvastatin, ezetimibe; acetylsalicylic acid, primary and secondary prevention, combination therapies.

Lipid disorders: an overview of the most preventable cardiovascular risk factor

Deaths worldwide are primarily related to cardiovascular diseases, among which atherosclerotic cardiovascular disease (ASCVD) plays a prominent role (20 million annually). In 2019, ASCVDs accounted for more than two-thirds of cardiovascular disease-related deaths overall (coronary artery disease [CAD] – 49.2%; ischaemic stroke – 17.7%; peripheral artery disease [PAD] – 0.4%) [1]. Invariably, for many years, the main risk factors for ASCVD, irrespective of gender, have included hypertension, poor dietary habits and lipid disorders (elevated low-density lipoprotein cholesterol [LDL-C]) [1–3]. At the American College of Cardiology (ACC) 2024 Congress in Atlanta, findings were presented indicating that more than 88% of CAD, the leading cause of death worldwide, is specifically related to the presence of inadequately controlled risk factors [4]. The global burden of CAD has steadily increased over the past three decades, in parallel with the escalation of risk factors [4].

The relationship between LDL-C concentration and ASCVD risk depends on the degree of increase in LDL-C concentration and the duration of exposure to this elevated concentration (called cholesterol-years) [2]. The theoretical cumulative threshold of LDL-C exposure, at which ACS is more likely to occur, has been set at approximately 8,000 mg/dl-years; such a threshold is reached at different ages depending on individual LDL-C levels and duration of exposure [5]. For example, the estimated age of onset of acute coronary syndrome (ACS) in a patient with LDL-C levels of 200 mg/dl, 125 mg/dl and 80 mg/dl is approximately 40, 60 and 100 years, respectively [5, 6]. Hence, in a patient with untreated heterozygous familial hypercholesterolaemia (HeFH) or lifestyle-related severe hypercholesterolaemia with a high baseline LDL-C, the mean age of onset of acute coronary syndrome (ACS) might be 40–45 and 55–60 years, respectively, and 70–75 years in the general population [5]. It is noteworthy that the risk of ACS depends on the cumulative exposure to LDL-C depending on the period in life when it started. The same cumulative exposure if it occurred in a younger person is associated with a higher risk of ACS than in an older

person [7]. This is crucial because lipid disorders are an important factor in premature myocardial infarction (which currently accounts for 25% of all ACS cases), defined as women < 55 years, men < 60 years [8]. A 50% reduction in LDL-C levels reduces cardiovascular risk irrespective of the duration of hypercholesterolaemia, but to the greatest extent when achieved at the earliest possible stage of the disease (starting treatment at age 30 – hazard ratio [HR] = 0.48; 40 – HR = 0.54; 50 – HR = 0.63; 60 years – HR = 0.73) [9]. Each 1 mmol/l reduction in serum LDL-C is associated with a 12% (95% CI: 8–16%) reduction in the risk of major cardiovascular events (MACE) in year 1, 20% (16–24%) in year 3, 23% (18–27%) in year 5 and 29% (14–42%) in year 7 of lipid-lowering treatment [10]. It should be emphasised that intensive lipid-lowering treatment (LLT) leading to LDL-C reduction < 40 mg/dl (< 1 mmol/l) is safe and does not increase the risk of neurocognitive impairment, cancer, haemorrhagic stroke, type 2 diabetes, hepatobiliary disorders, muscular impairment or cataracts, while it allows an even greater reduction in the risk of cardiovascular events (OR = 0.82; 95% CI: 0.72–0.94) [11].

In primary prevention, LLT is associated with a reduction in the risk of death from any cause by 11%, death from cardiovascular causes by 20%, ACS by 38%, stroke by 17%, unstable ischaemic heart disease (IHD) by 25% and MACE by 26% [12]. In secondary prevention, LLT leads to a reduction in the risk of death from any cause by 22%, death from cardiovascular causes by 31%, ACS by 38%, the need for coronary revascularisation by 44% and cerebrovascular events by 25% [13]. The above information clearly shows that the treatment of lipid disorders should be carried out according to the principles continuously advocated for the last several years by, among others, the International Lipid Expert Panel (ILEP) and the Polish Lipid Association (PoLA): “the earlier the better”, “the lower the better” and “the longer the better” [14]. Only such an approach allows the maximum reduction of exposure to elevated LDL-C over the life course. It is noteworthy that lipid disorders are the most preventable risk factor for ASCVD, allowing risk reductions of up to 60% assuming early achievement of the therapeutic goal and maintenance throughout lifetime. In 1990, 3 million people died

worldwide due to high LDL-C levels, and in 2019, 4.4 million people [15]. If, hypothetically, patients had a therapeutic target of LDL-C set, there would be a reduction of 4.4 million deaths per year worldwide and up to 30–40,000 only in Poland [16].

Rosuvastatin and ezetimibe SPC treatment – when and in whom?

The target level of lipid parameters depends on the individual cardiovascular risk of each patient (Tables I and II) [14, 17].

The 2019 Guidelines of the European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) indicate that in high and very high cardiovascular risk patients, the target LDL-C level

should be < 55 mg/dl (1.5 mmol/l; including a reduction in baseline level by ≥ 50%) and < 70 mg/dl (1.8 mmol/l; including a reduction in baseline concentration by ≥ 50%), respectively – Class I recommendations [18]. The pharmacological treatment recommendations correspond fully with this, as they indicate that a potent statin should be used at the highest tolerated dose to achieve the target LDL-C level (Class I recommendations). In high-risk and very high-risk patients, when monotherapy with a potent statin at the highest tolerated dose does not achieve the therapeutic goal, ezetimibe should be added (Class I recommendations) [18]. This means that the EAS/ESC 2019 guideline, as well as the subsequent ESC guidelines on prevention of cardiovascular dis-

Table I. Cardiovascular risk categories with definitions [14, 17]

Cardiovascular risk categories	Definition
Extreme	Patient in primary prevention with SCORE2 > 25% ¹ ; post-acute coronary syndrome (ACS) and another vascular event in the last 2 years; post-acute coronary syndrome and the presence of peripheral artery disease or polyvascular disease ² (multilevel atherosclerosis); post-acute coronary syndrome and concomitant multivessel coronary artery disease; post-acute coronary syndrome and familial hypercholesterolaemia; post-acute coronary syndrome in a patient with diabetes and at least one additional risk factor (elevated Lp(a) > 50 mg/dl > 125 nmol/l or hsCRP > 3 mg/l or chronic kidney disease [eGFR < 60 ml/min/1.73 m ²]).
Very high	Cardiovascular disease documented clinically or by imaging examinations; diabetes mellitus with organ damage ³ or other major risk factors ^{4,5} , early onset type 1 diabetes mellitus lasting > 20 years; chronic kidney disease with eGFR < 30 ml/min/1.73 m ² ; familial hypercholesterolaemia with cardiovascular disease or another major risk factor ⁵ ; very high risk according to SCORE2 or SCORE-2-OP for gender and age.
High	Significantly elevated single risk factor, especially TC > 310 mg/dl (> 8 mmol/l), LDL-C > 190 mg/dl (> 4.9 mmol/l), or blood pressure ≥ 180/110 mm Hg; familial hypercholesterolaemia without other risk factors; diabetes mellitus without organ damage (regardless of duration) ⁶ ; chronic kidney disease with eGFR 30–59 ml/min/1.73 m ² ; high risk according to SCORE2 or SCORE-2-OP for gender and age.
Moderate	Low to moderate risk according to SCORE2 or SCORE-2-OP for gender and age.
Low	Risk of < 1% according to Pol-SCORE/SCORE.

¹SCORE2 risk > 25% corresponds to e.g. woman aged 65 years, smoking, with a systolic blood pressure of 165 mm Hg and non-HDL cholesterol of 155 mg/dl (4 mmol/l) or man aged 60 years, smoking, with a systolic blood pressure of 165 mm Hg and non-HDL cholesterol of 194 mg/dl (5 mmol/l); estimated LDL-C > 160 mg/dl (4.1 mmol/l). ²Polyvascular disease (= multilevel atherosclerosis) – the presence of significant atherosclerotic lesions in at least two of the three vascular beds – coronary vessels, carotid and vertebral arteries and/or peripheral vessels. ³Organ damage is defined as the presence of microalbuminuria, retinopathy, neuropathy and/or left ventricular myocardial damage. ⁴Other means at least 2. ⁵Major risk factors are age ≥ 65 years, hypertension, dyslipidaemia, smoking, obesity; not applicable to type 1 diabetes in young adults (< 35 years of age) with diabetes duration of < 10 years. When assessing renal function, it is recommended to determine albuminuria using the albumin/creatinine ratio (ACR).

Table II. Therapeutic targets by cardiovascular risk category [14, 17]

Risk categories	Primary target LDL-C	Equivalent primary target non-HDL-C	Equivalent primary target ApoB	Secondary target TG
Extreme	< 40 mg/dl (< 1.0 mmol/l)	< 70 mg/dl (< 1.8 mmol/l)	< 55 mg/dl	< 100 mg/dl
Very high	< 55 mg/dl (< 1.4 mmol/l) and a reduction of the baseline level by ≥ 50%	< 85 mg/dl (< 2.2 mmol/l)	< 65 mg/dl	(< 1.1 mmol/l)
High	< 70 mg/dl (< 1.8 mmol/l) and a reduction of the baseline level by ≥ 50%	< 100 mg/dl (< 2.5 mmol/l)	< 80 mg/dl	
Moderate	< 100 mg/dl (< 2.5 mmol/l)	< 130 mg/dl	< 100 mg/dl	
Low	< 115 mg/dl (< 3.0 mmol/l)	(< 3.4 mmol/l)		

ease (2021) [19], indicate step-by-step intensification of lipid-lowering treatment. The Polish Lipid Association (PoLA) 2021 guidelines elaborate the definition of patients with extreme cardiovascular risk and propose a more intensive treatment. The PoLA guidelines, in line with the recommendations of the International Lipid Expert Panel (ILEP) of April 2021 [20], indicate that in extreme (see extended definition in Table I) and very high-risk patients, in whom it is known in advance that monotherapy with a potent statin will not achieve the therapeutic goal (in most of the patients), immediate/upfront treatment with a combination of a potent statin at the maximum tolerated dose with ezetimibe should be applied [14, 20]. This is because each of these patient groups needs to reach therapeutic targets as early as possible, in order to minimise their cumulative lifetime exposure to elevated LDL-C levels [2]. The 2023 ESC guidelines for the management of ACS contain a slightly modified recommendation for lipid-lowering treatment. Drawing on, inter alia, the work of the Polish experts, it was recommended that upfront combination therapy with a potent statin + ezetimibe may be considered in ACS patients (recommendation class IIb) [21].

The latest 2024 ILEP recommendations for lipid-lowering treatment in very high CVD risk patients have introduced significant modifications to treatment [22]. In patients with established ASCVD prior to any cardiovascular event (without ACS, HeFH, extreme cardiovascular risk, diabetes or statin intolerance), it is recommended to administer upfront lipid-lowering treatment with a combination of a potent statin at the maximum tolerated dose and ezetimibe, preferably in the form of a single pill combination (SPC). In patients at extreme cardiovascular risk, the ILEP 2024 guidelines advocate upfront lipid-lowering therapy with triple SPC including a potent statin at the maximum tolerated dose with ezetimibe and inhibitors/modulators of proprotein convertase subtilisin/kexin type 9 (PCSK9 inhibitors and inclisiran) or a statin with ezetimibe and bempedoic acid (obviously if available and possible based on the country-specific reimbursement criteria). The ILEP 2024 guidelines also include precise recommendations for the personalisation of LLT in patients with partial/complete statin intolerance or metabolic disorders [22]. This is new, as the ESC/EAS guidelines of 2019 [18] as well as the ESC ACS guidelines of 2023 [21] or the most recent guidelines for the management of chronic coronary syndromes (2024) [23] recommend a stepwise intensification of lipid-lowering treatment (starting with a statin, then adding ezetimibe if the target is not reached after 4–6 weeks and in the next step adding a PCSK9 inhibitor, inclisiran or bempedoic acid) [18, 21, 23]. The approach recommended by

ILEP 2024 is much closer to daily clinical practice and has much greater benefits for patients (faster achievement of the target, fewer treatment discontinuations and side effects, greater CVD risk reduction), as clearly demonstrated in clinical trials and their meta-analyses [24].

In a registry study involving 72,050 patients undergoing percutaneous coronary intervention (PCI), which assessed the effect of rosuvastatin monotherapy compared with rosuvastatin + ezetimibe combination therapy on the risk of occurrence of a composite endpoint (3-year composite event encompassing cardiovascular death, ACS, coronary revascularisation, hospitalisation for heart failure or non-fatal stroke), upfront combination LLT was found to be associated with a lower risk of the composite endpoint (HR = 0.75; 95% CI: 0.7–0.79), lower risk of treatment discontinuation (HR = 0.85; 95% CI: 0.78–0.94) and lower risk of new cases of diabetes (HR = 0.80; 95% CI: 0.72–0.88) [25]. Extremely important clinical guidance was provided by a study by Lewek *et al.* involving 38,023 ACS patients from the Polish Registry of Acute Coronary Syndromes (PL-ACS). The study showed that initial combination therapy (potent statin + ezetimibe) was associated with a significant reduction in all-cause mortality compared with strong statin monotherapy (OR = 0.53; 95%CI: 0.38–0.733, with an absolute risk reduction of 4.7% at 3 years (number needed to treat [NNT] = 21), and a significant effect was observed after only 52 days of treatment [26]. A study by Jang *et al.* involving 21,446 ACS patients also demonstrated a significant advantage of initial statin + ezetimibe combination treatment, finding that this approach reduced the risk of ACS, stroke and all-cause mortality by 15% (HR = 0.85; 95% CI: 0.78–0.92) compared with statin monotherapy [27]. A meta-analysis of six randomised clinical trials (RCTs) by Oliveira *et al.*, involving 2,574 ACS patients, confirmed that combination treatment (statin + ezetimibe) has greater cardiovascular benefits: an additional 7% reduction in the risk of MACE (RR = 0.93; 95% CI: 0.90–0.97) and non-fatal ACS by 12% (RR = 0.88; 95% CI: 0.81–0.95) [28]. It is also worth mentioning that statin + ezetimibe combination therapy may have benefits in primary prevention (prevention of first MACE). A study by Jun *et al.* involving 69,488 participants showed that the use of statin + ezetimibe combination therapy compared with statin monotherapy in at-risk patients in primary prevention led to a 19% risk reduction: ACS (HR = 0.81; 95% CI: 0.71–0.94) and stroke by 22% (HR = 0.78; 95% CI: 0.65–0.93) [29].

A meta-analysis of 14 studies (11 randomised controlled trials and 3 cohort studies) with 108,353 very high-risk patients showed that combination LLT significantly more effectively reduced

the LDL-C level from baseline (MD, -12.96 mg/dl, 95% CI: -17.27 to -8.65), and significantly reduced all-cause mortality (OR = 0.81, 95% CI: 0.67 to 0.97), MACE (OR = 0.82, 95% CI: 0.69 to 0.97), and stroke incidence (OR = 0.83 95% CI: 0.75 to 0.91), when compared with statin monotherapy. The risk of adverse events and the therapy discontinuation rate were comparable between groups, and even significantly reduced (discontinuation by 44% for moderate intensity statin and ezetimibe) in the accompanying network meta-analysis [24]. A meta-analysis of five studies by Damarpally *et al.* including 48,668 patients with ACS showed that potent statin monotherapy was associated with higher mortality compared to statin + ezetimibe combination treatment (RR = 1.32; 95% CI: 1.18–1.47) [30]. Another meta-analysis of 12 studies by Shaya *et al.* demonstrated that after 6 months of combined statin + ezetimibe therapy versus statin monotherapy, a significantly greater reduction in LDL-C was observed in patients with ASCVD (-21.86 mg/dl; 95% CI: -26.56 to -17.17) as well as in ACS patients (-19.19 mg/dl; 95% CI: -25.22 to -13.16) [31]. The use of statin + ezetimibe combination therapy also significantly increases the chance of achieving target LDL-C levels (by as much as 85%) [24, 32].

The more beneficial cardiovascular effects associated with statin + ezetimibe combination therapy are due to the synergistic (and not just additive) anti-atherosclerotic effects of these medicines. Statins reduce LDL-C levels, have antioxidant, anti-inflammatory and anticoagulant effects and can dissolve cholesterol crystals. Ezetimibe, on the other hand, also lowers LDL-C level (although through a different mechanism of action), has an antioxidant effect, reduces sterols, inhibits vascular smooth muscle cell proliferation and causes cholesterol crystals to dissolve [33]. The results of the abovementioned studies and the recent ILEP 2024 recommendations [22] should put an end to the debate over the rationale for starting lipid-lowering therapy with a potent statin at the maximum tolerated dose in combination with ezetimibe in patients who are at least at very high cardiovascular risk. Such management significantly improves the prognosis of these patients and should be the gold standard of treatment [34]. Unfortunately, despite the clear evidence of the enormous cardiovascular benefits and safety of lipid-lowering treatment, data indicate that the achievement of the LDL-C therapeutic goal as well as the use of combination therapy in high- and very high-risk patients is low. The SANTORINI study, which enrolled 9,044 patients at high or very high cardiovascular risk (from 14 Western European countries), found that only 20.1% of these patients (24% in the high-risk group and 18.6% in the very high-risk group) achieved the

therapeutic goal according to the 2019 ESC/EAS guidelines [18, 35]. During the extended follow-up of the SANTORINI trial, the use of monotherapy and combination therapy increased from 53.6 and 25.6% to 57.1 and 37.9%, respectively. The mean LDL-C level decreased from 2.4 to 2.0 mmol/l. Goal attainment according to the 2019 EAS guidelines [18] improved from 21.2 to 30.9%, largely driven by LLT use among those not on LLT at baseline. LDL-C goal attainment was greater with combination therapy compared with monotherapy at follow-up (39.4 vs. 25.5%) [36].

From a clinical point of view, it is important to specify which strong statin should be used to start the treatment. Potent statins include rosuvastatin, atorvastatin and pitavastatin (according to the International Atherosclerosis Society [IAS], while Polish guidelines classify pitavastatin as having moderate to intense potency) [37, 38]. A comparison of the lipid-lowering efficacy of different statins resulted in the following ranking of their power to reduce LDL-C: rosuvastatin > atorvastatin > pitavastatin > simvastatin > pravastatin > fluvastatin > lovastatin > placebo. Rosuvastatin ranked first in terms of its efficacy to lower LDL-C and apolipoprotein B (apoB) levels and its power to increase apolipoprotein A1 (apoA1) levels [39]. Interestingly, when looking at the anti-inflammatory properties (effect on hsCRP), the order is slightly different, with rosuvastatin having the strongest anti-inflammatory effect, followed by fluvastatin, pitavastatin, atorvastatin, pravastatin, simvastatin and lovastatin [40]. Rosuvastatin is, according to the U.S. Food and Drug Administration (FDA), the most effective statin (by 4–6%) in reducing LDL-C concentrations versus double-dose atorvastatin. The EAS/ESC, PoLA 2021, ESC 2024 and ILEP 2024 guidelines all agree that the statin of first choice is the one with the greatest lipid-lowering potency [14, 18, 21, 22]. According to the PoLA 2021 guidelines, atorvastatin is preferred in patients with chronic kidney disease [14]. The ASTEROID trial showed that rosuvastatin administered for 24 months at a dose of 40 mg led to regression of atherosclerotic coronary artery lesions (10.16 mm² vs. 5.81 mm²) [41]. The SATURN study compared the effects of the highest doses of rosuvastatin and atorvastatin on atherosclerotic lesion progression. It showed that rosuvastatin had a higher lipid-lowering potency, while the effect on plaque volume reduction was similar for both statins tested [42]. Nevertheless, a meta-analysis of six RCTs by Kumar *et al.* showed that rosuvastatin reduced plaque volume and LDL-C concentration to a greater extent than atorvastatin [43]. Some risk of new cases of diabetes (NOD) is associated with the use of potent statins [44]. This risk can be optimised using statin combination therapy with ezetimibe (diminished risk of dia-

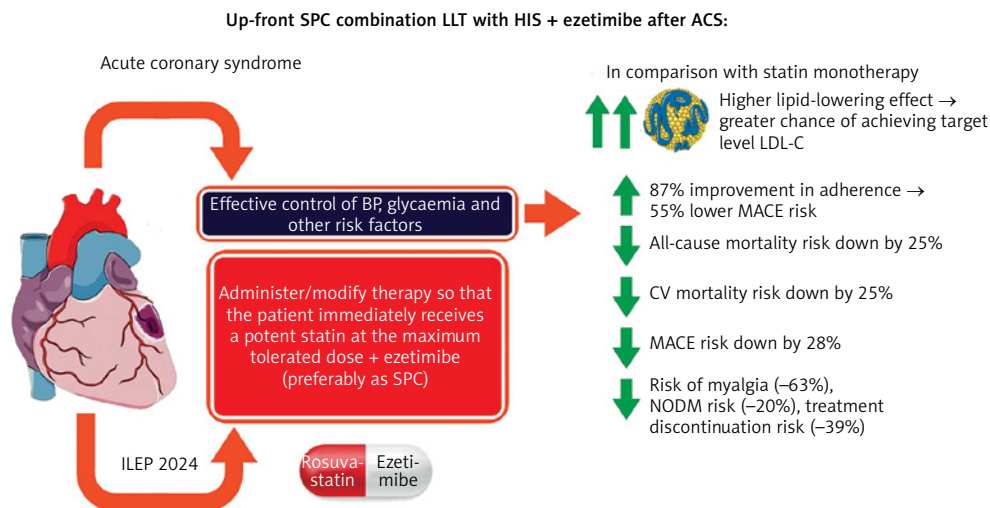


Figure 1. Benefits of up-front administration of SPC with a potent statin at the maximum tolerated dose and ezetimibe in a patient with acute coronary syndrome. Study authors based the figure on information from multiple sources [22, 24, 25, 47, 49]

IILEP – International Lipid Expert Panel, ACS – acute coronary syndrome, LDL-C – low-density lipoprotein cholesterol, CV – cardiovascular, MACE – major cardiovascular adverse event.

betes with improving LDL-C and outcomes reduction). The beneficial effect was demonstrated in the RACING trial, in which patients after PCI were given rosuvastatin (20 mg) in monotherapy versus rosuvastatin (10 mg) with ezetimibe. After 3 years, it was found that combination therapy was associated with a lower incidence of new cases of diabetes requiring pharmacotherapy (7.7% vs. 9.6%; HR = 0.80; 95% CI: 0.72–0.88). Furthermore, combination therapy was found to be better tolerated by patients, as discontinuation of treatment was observed significantly less frequently (6.5% vs. 7.6%; HR = 0.85; 95% CI: 0.78–0.94) [45]. Combination therapy with a statin and ezetimibe compared with monotherapy is significantly less likely to cause myalgia (RR = 0.27; 95% CI: 0.13–0.57), which means better therapy adherence and a significantly lower risk of treatment discontinuation related to adverse effects (RR = 0.61; 95% CI: 0.51–0.74) [46, 47]. It is worth pointing out that when statin substitution is needed (in patients with statin-associated muscle symptoms), rosuvastatin can be switched to atorvastatin without significant loss of cardiovascular protection [48]. The above observation was important in the de-

velopment of the new IILEP 2024 recommendations, in which for patients with metabolic disorders (including diabetes) and patients with statin intolerance it is recommended to start treatment with a lower (not maximum) dose of statin (e.g. rosuvastatin 20 mg instead of 40 mg) along with ezetimibe, allowing the achievement of the therapeutic goal with fewer side effects and discontinuations and better adherence; this approach also may improve treatment of patients with suboptimal lipid-lowering therapy [22].

The guidelines rightly indicate that combination LLT should be based on SPCs as much as possible. It was demonstrated beyond any doubt that patients taking a statin with ezetimibe as an SPC, compared to those taking both medicines in the same doses in separate pills, had an 87% (RR = 1.87; 95% CI: 1.75–1.99) higher chance of good adherence. And, in turn, patients with high adherence had a 55% (RR = 0.45; 95% CI: 0.25–0.80) lower risk of cardiovascular events (cardiovascular mortality or cardiovascular hospitalisation) [49].

The benefits of upfront SPC lipid-lowering treatment with a potent statin at the maximum tolerated dose and ezetimibe in patients with ACS

Table III. Recommendations for the use of rosuvastatin and ezetimibe SPC

Expert opinion
<ul style="list-style-type: none"> • Combination lipid-lowering therapy with SPC of rosuvastatin and ezetimibe should be considered (IIa) in patients at high cardiovascular risk who do not achieve target LDL-C level with the maximum tolerated statin dose. In this group of patients, (IIb) upfront combination lipid-lowering therapy may be considered.
<ul style="list-style-type: none"> • Combination treatment with SPC of rosuvastatin and ezetimibe is recommended (IB) as a first-line treatment in all patients at very high cardiovascular risk, primarily for secondary prevention.
<ul style="list-style-type: none"> • Combination treatment with SPC of rosuvastatin and ezetimibe and PCSK9 inhibitor/inclisiran should be considered as early as possible in all patients at extreme cardiovascular risk (IIa).

SPC – single pill combination, LDL-C – low-density lipoprotein cholesterol, PCSK9 (proprotein convertase subtilisin-kexin type 9).

are summarised in Figure 1, while recommendations for the use of SPC (in this case rosuvastatin + ezetimibe) are presented in Table III.

Combination treatment with SPC of rosuvastatin and acetylsalicylic acid – when and for whom?

The use of acetylsalicylic acid (ASA) in cardiovascular prevention, especially primary prevention (prior to ASCVD), is still widely debated [50]. In the course of ASCVD and diabetes, impaired vascular

endothelial function, excessive platelet reactivity and unfavourable atheroma remodelling resulting in a more atherothrombogenic environment are observed [51]. According to the 2021 ESC guidelines for cardiovascular prevention, ASA 75–100 mg/day is recommended for secondary prevention (recommendation class IA). For primary prevention, the ESC 2021 guidelines state that low-dose ASA may be considered for primary prevention in patients with diabetes and a high or very high risk of ASCVD, if there are no clear contraindications

Table IV. Selected recommendations of the European Society of Cardiology (ESC) on the use of acetylsalicylic acid in various diseases [21, 23, 52–54].

RECOMMENDATION	Class	Level
Primary prevention		
In patients with diabetes and a high or very high risk of ASCVD, low-dose ASA may be considered for primary prevention in the absence of clear contraindications.	IIb	A
Secondary prevention		
ASA at a dose of 75–100 mg/day is recommended for secondary prevention.	I	A
Patients with diabetes		
In adults with type 2 diabetes without a history of symptomatic ASCVD or revascularisation, ASA (75–100 mg once daily) may be considered to prevent the first severe vascular event, in the absence of clear contraindications.	IIb	A
ASA at a dose of 75–100 mg once daily is recommended in patients with diabetes and previous myocardial infarction or revascularisation (CABG or stenting).	I	A
Diseases of the peripheral arteries and aorta		
In patients with asymptomatic PAD and diabetes, aspirin (75–100 mg) may be considered for primary prevention, unless contraindicated.	IIb	A
Antiplatelet therapy with aspirin alone (in the range of 75–160 mg once daily) or clopidogrel alone (75 mg once daily) is recommended to reduce MACE in patients with symptomatic PAD.	I	A
Combination treatment with rivaroxaban (2.5 mg twice daily) and aspirin (100 mg once daily) should be considered for patients with PAD, a high risk of ischaemia and a low risk of bleeding.	IIa	A
Combination treatment with rivaroxaban (2.5 mg twice daily) and aspirin (100 mg once daily) should be considered in patients with PAD and a low risk of bleeding after lower limb revascularisation.	IIa	B
In patients with asymptomatic > 50% carotid artery stenosis, long-term antiplatelet therapy (usually low-dose aspirin) should be considered if the risk of bleeding is low.	IIa	C
In patients with atherosclerotic renal artery stenosis, low-dose aspirin may be considered.	IIb	C
Chronic coronary syndromes		
In patients with CCS without previous myocardial infarction or revascularisation, but with evidence of significant obstructive coronary artery disease, aspirin 75–100 mg daily is recommended for life-long use.	I	B
After CABG, aspirin is recommended at a dose of 75–100 mg daily for life-long use.	I	A
In patients with CCS after myocardial infarction or after remote PCI, aspirin 75–100 mg daily is recommended for life-long use after initial DAPT.	I	A
Acute coronary syndromes		
Aspirin is recommended for all patients without contraindications at an initial oral dose of 150–300 mg (or 75–250 mg intravenously) and a maintenance dose of 75–100 mg/day orally for long-term treatment.	I	A
Aspirin is not recommended for cancer patients with platelet counts < 10,000/μl.	III	C

ASA – acetylsalicylic acid, ASCVD – atherosclerotic cardiovascular disease, CABG – coronary artery bypass grafting, PAD – peripheral artery disease, MACE – major adverse cardiovascular event, CCS – chronic coronary syndrome, PCI – percutaneous coronary intervention, DAPT – dual antiplatelet therapy.

(recommendation class IIb A) [19]. It is recommended that a proton pump inhibitor (PPI) should be considered in patients receiving ASA and at increased risk of gastrointestinal bleeding (recommendation class IA) [19]. Antiplatelet therapy is not recommended in patients with low/moderate cardiovascular risk due to an increased risk of major bleeding (unfavourable balance of benefits and risks) (recommendation class IIIA) [19]. Selected ESC recommendations for the use of ASA in the treatment of certain diseases are summarised in Table IV [19, 21, 23, 52, 53].

In primary prevention, the ESC 2021 guidelines [19] (and earlier US guidelines [54]) state that ASA use may be considered, after weighing potential benefits and risks, in patients with diabetes and high/very high cardiovascular risk. This recommendation is based on studies that show inconclusive evidence of significant benefits of using aspirin in primary prevention (Figure 2). Due to this inconclusive evidence on the ASA benefits in primary prevention, it is important to identify more specific patients at risk who might

really benefit from this therapy. Available studies suggest that coronary computed tomography angiography (CCTA) with the calcium score (CS) may also be helpful in decision making, indicating that for a CAC-Score (coronary artery calcium score) > 100 there are significant benefits of using aspirin in the primary prevention of cardiovascular incidents, which has been confirmed in many studies [55]. A study by Ajufo *et al.* involving 2,191 participants in primary prevention showed that a higher CAC score was associated with an increased risk of bleeding and more clearly with ASCVD risk [56]. Compared with participants from the lowest CAC score group, those in the group with the highest CAC had an unadjusted hazard ratio (HR) of 2.6 (95% CI: 1.5–4.3; $p < 0.001$) for bleeding events and 5.3 (95% CI: 3.6–7.9; $p < 0.001$) for ASCVD events. After multivariable adjustment for risk factors, the association between CAC and bleeding became weaker (CAC ≥ 100 vs. CAC = 0; HR = 1.5, 95% CI: 0.8–2.6; $p = 0.19$), but the association between CAC and ASCVD remained significant in all CAC categories considered. There were no

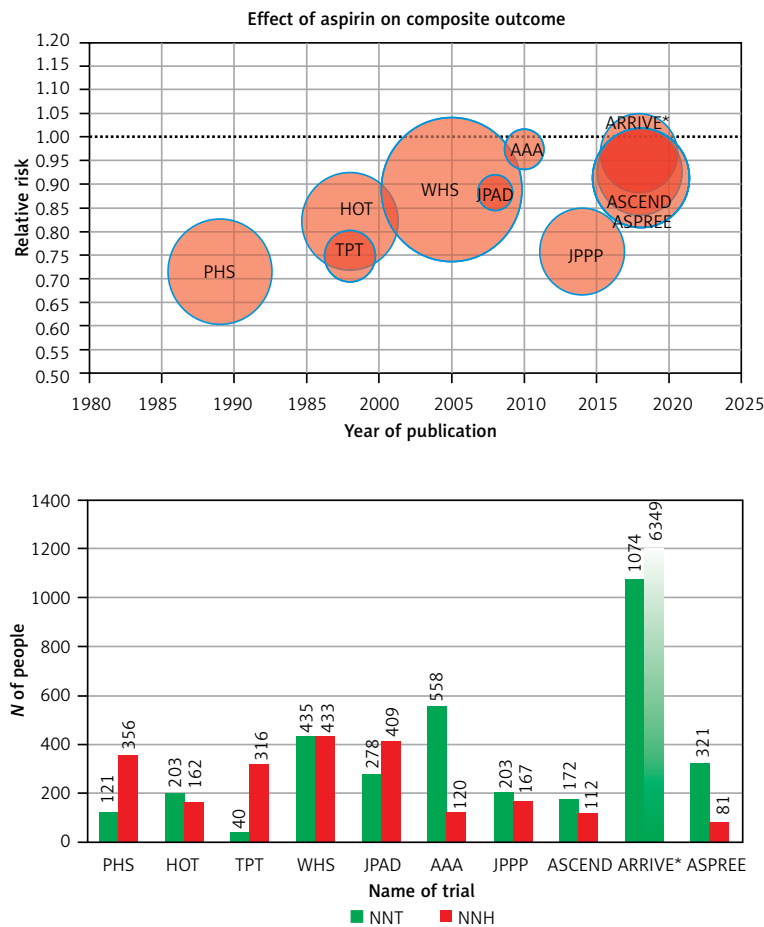


Figure 2. Summary of studies on the effect of aspirin use in primary prevention and the ratio of benefits (number needed to treat – NNT) to risks of adverse effects (number needed to harm – NNH). Based on: Della Bona R, Giubilato S, Palmieri M. *et al.* J Clin Med 2024; 13: 4148. <https://doi.org/10.3390/jcm13144148> (reprint permission not required: CC BY licence) [50]

differences in the association of CAC with bleeding or ASCVD according to age above and below 50 years, black and non-black race, and male vs. female gender. Based on the obtained results, the authors concluded that people with CAC-Score > 100 and low bleeding risk can achieve significant cardiovascular benefits from taking ASA [56].

Thus, it is recommended that ASA in primary prevention should be considered in particular in patients with CAC \geq 100, an increased risk of ASCVD (\geq 5%) and aged < 70 years [55].

It is worth citing here the 2019 cardiovascular prevention guidelines developed by the American College of Cardiology and the American Heart Association (ACC/AHA), recommending that low-dose ASA (7–100 mg orally daily) may be considered for primary prevention of ASCVD among selected adults aged 40 to 70 years who are at higher ASCVD risk but not at increased bleeding risk (recommendation class IIb A) [54]. At the same time, ACC/AHA 2019 advocates that low-dose aspirin (75–100 mg orally daily) should not be administered on a routine basis for primary prevention of ASCVD in adults > 70 years of age and adults of any age at an increased risk of bleeding (class III recommendation) [54].

In patients with diabetes, the use of ASA in primary prevention was associated with a significant 8% reduction in the risk of MACE, with a concomitant overall increase in the risk of major bleeding by 30% and the risk of major gastrointestinal bleeding by 39% [57]. The randomised ASCEND trial involving 15,480 patients with diabetes who received ASA vs. placebo for 7.4 years showed a significant 12% reduction in the risk of MACE (RR = 0.88; 95% CI: 0.79–0.97). The risk of major bleeding went up by 29% (RR = 1.29; 95% CI: 1.09–1.52) [58]. A 9% reduction in the risk of MACE (OR = 0.91; 95% CI: 0.84–0.99) was also found in a meta-analysis of eight studies by Ma *et al.*, including 32,024 patients with diabetes [59]. A meta-analysis of 10 randomised clinical trials by Wang *et al.* showed that ASA use was associated with a significant reduction in the risk of MACE (RR = 0.89; 95% CI: 0.84–0.93), ACS (RR = 0.86; 95% CI: 0.78–0.95) and ischaemic stroke (RR = 0.84; 95% CI: 0.76–0.93); however, ASA also increased the risk of adverse events, i.e. major bleeding (RR = 1.42; 95% CI: 1.26–1.60), intracranial haemorrhage (RR = 1.33; 95% CI: 1.11–1.59) and gastrointestinal bleeding (RR = 1.91; 95% CI: 1.44–2.54). A more pronounced risk reduction in primary prevention was found in high-risk patients, those with diabetes and those aged \leq 70 years [60]. The use of ASA in primary prevention may provide cardiovascular benefit only in patients with at least high cardiovascular risk (12% reduction in MACE [OR = 0.88; 95% CI: 0.80–0.97]) [61].

The use of a two-drug SPC containing rosuvastatin and ASA in patients for whom such treatment is indicated significantly improves cardiovascular prognosis. A study by Liu *et al.* including 3,778 individuals from the NHANES 2011–2018 database showed that rosuvastatin with ASA versus ASA monotherapy led to a 56% reduction in the risk of ASCVD (OR = 0.34; 95% CI: 0.23–0.50) in primary prevention [62]. It is worth noting that in elderly patients without ASCVD to whom ASA was administered despite a clear indication for such treatment, its discontinuation remains safe and does not increase cardiovascular risk in the short or long term [63].

Lp(a) – an additional argument for the use of aspirin in primary prevention?

The cardiovascular benefits observed as a result of ASA use in patients with diabetes are due to the residual risk of ASCVD [64]. Residual ASCVD risk consists of suboptimal LDL-C reduction, low-grade inflammation, prothrombotic factors, elevated triglycerides, elevated lipoprotein (a) (Lp(a)) and inadequate glycaemic control [64, 65]. ASA contributes to the optimisation of ASCVD risk through its effects on prothrombotic factors and, as recently shown, also on Lp(a). Studies to date on the use of aspirin in the context of prothrombotic risk associated with elevated Lp(a) concentrations have been inconclusive. However, the existence of such properties is beyond doubt, as the Lp(a) molecule is similar in structure to plasminogen. This is confirmed, for example, by the LIP(a)R registry, which demonstrated an independent association between increased Lp(a) levels (> 30 mg/dl/75 nmol/l) and platelet counts in patients at very high cardiovascular risk in secondary prevention [66].

Hence, a new potential indication to consider ASA for primary prevention is an elevated lipoprotein (a) [Lp(a)] level. A recent analysis of the Multi-Ethnic Study of Atherosclerosis (MESA) by Bhatia *et al.* involving 2,183 patients without a history of ASCVD showed that ASA use was associated with a significant 46% reduction in ASCVD risk among patients with elevated Lp(a) levels > 50 mg/dl (125 nmol/l) (HR = 0.54; 95% CI: 0.32–0.94). Those with Lp(a) levels > 50 mg/dl who used ASA had a similar ASCVD risk to those with Lp(a) levels \leq 50 mg/dl, regardless of aspirin use [67]. Similar data were provided by a study by Razavi *et al.* involving 2,990 individuals from the National Health and Nutrition Examination Survey (NHANES III, 1988–1994) without a history of ASCVD. They found that regular ASA use was associated with a 52% lower risk of ASCVD mortality in those with Lp(a) levels > 50 mg/dl (HR = 0.48; 95% CI: 0.28–0.83), but not in those without ele-

vated Lp(a) levels (HR = 1.01, 95% CI: 0.81–1.25) [68]. The results of this study are highly relevant because up to one in every 4–5 patients in Poland has an elevated Lp(a) level, i.e. > 6 million people [69]. It has been shown that among patients treated in Polish cardiology outpatient clinics, the prevalence of elevated Lp(a) levels is about 22%, and among patients with hyperlipidaemia it is 28% [70]. Notably, Lp(a) is an ASCVD risk factor independent of LDL-C (5-fold more atherogenic), whose concentration is mainly genetically determined [71, 72]. The launch of medicines targeting Lp(a) – pelacarsen, olpasiran, zerlasiran, lepodisiran and muvalaplin – is expected [72, 73]. Considering the use of ASA in patients at least at high cardiovascular risk in primary prevention with elevated Lp(a) levels may help to optimise the ASCVD risk associated with it.

Table V and Figure 3 summarise the proposed recommendations for use of the two-drug SPC of rosuvastatin + ASA in cardiovascular prevention [74].

Summary and conclusions

Combination drugs, preferably as SPC, that improve adherence to treatment and achievement of therapeutic goals and help to reduce cardiovascular incidents and mortality are undoubtedly a way to improve poor treatment outcomes in Poland, where cardiovascular disease is responsible for up to 200,000 deaths per year, with the number of myocardial infarctions and strokes reaching 80,000 annually, 25% of people dying within 3 years after myocardial infarction and, finally, only 20–25% of patients at high or very high cardiovascular risk achieving the therapeutic target for LDL cholesterol. This expert opinion paper is intended to serve as practical guidance to optimise treatment for patients who have indications for lipid-lowering and antiplatelet therapy (up to several million people in Poland) using available rosuvastatin-based combination drugs. In this context, it should be emphasised that it is not possible to establish clear recommendations

Table V. Summary of recommendations for the use of the rosuvastatin + acetylsalicylic acid (ASA) combination in patients for primary and secondary prevention

Expert opinion
<p>PRIMARY PREVENTION</p> <ul style="list-style-type: none"> • The use of ASA is not recommended for primary prevention in patients at low/moderate cardiovascular risk, regardless of the concomitant elevated Lp(a) (III) levels. • Low-dose ASA (75–100 mg orally daily) in combination with rosuvastatin (SPC) may be considered (IIb) for primary prevention of ASCVD in adults aged < 70 years, with at least high cardiovascular risk and without increased bleeding risk*. • For primary prevention in at least high-risk patients with elevated Lp(a) levels (> 50 mg/dl/> 125 nmol/l), the combination of acetylsalicylic acid with rosuvastatin (SPC) should be considered (IIa). • In primary prevention, in patients with at least high risk and CAC-Score > 100, there is clinical evidence for an important role of aspirin in the prevention of cardiovascular incidents. In these patients, the use of SPC of rosuvastatin at an appropriate dose with aspirin should be considered (IIa). • In primary prevention, in patients with at least high cardiovascular risk, the decision to choose SPC of rosuvastatin with aspirin or ezetimibe is ultimately left to the discretion of the treating physician and is an important part of treatment personalisation. • Before administering ASA for primary prevention, the balance of benefits (cardiovascular risk reduction) and risks (risk of major bleeding) should always be carefully assessed; following ASA administration, a proton pump inhibitor should be considered in a group with increased risk of bleeding complications.
<p>SECONDARY PREVENTION</p> <ul style="list-style-type: none"> • In patients in secondary prevention with indications for the administration of ASA, treatment with SPC of rosuvastatin and ezetimibe (IIa) should be given priority, due to the greater CVD benefit of optimising the lipid profile and the more favourable safety profile. Aspirin in this case should be given as monotherapy unless a three-drug SPC of rosuvastatin + ezetimibe + ASA is available. • In patients in secondary prevention, excluding post-incident patients, the choice of SPC of rosuvastatin with aspirin or ezetimibe is ultimately left to the discretion of the treating physician and is an important part of treatment personalisation. • Indications for the use of ASA and modifications to antiplatelet treatment should be in accordance with the current European Society of Cardiology guidelines for specific diseases.
<p>GENERAL</p> <ul style="list-style-type: none"> • In patients receiving ASA, with an increased risk of bleeding complications, a proton pump inhibitor (I) is recommended to reduce the risk of serious bleeding.

ASA – acetylsalicylic acid, SPC – single pill combination, LDL-C – low-density lipoprotein cholesterol, PCSK9 – proprotein convertase subtilisin-kexin type 9.

*High risk of bleeding should be defined as: history of gastrointestinal bleeding or active peptic ulcer disease within the last 6 months, active liver disease (such as cirrhosis or active hepatitis) or history of aspirin intolerance; caution should also be exercised in the case of: malignancy diagnosed in the last 12 months, history of haemorrhagic or ischaemic stroke in the last 6 months, haemoglobin < 11 g/dl, thrombocytopenia < 100,000/μl and severe chronic kidney disease (GFR < 30 ml/min) [52, 74].

for the use of these combination therapies in individual patient groups, as data are still lacking (especially for combinations with aspirin) or are ambiguous in many cases, and in other cases there is an overlap of indications, which also points to the important role of treatment personalisation for patients at high and very high cardiovascular risk.

Acknowledgments

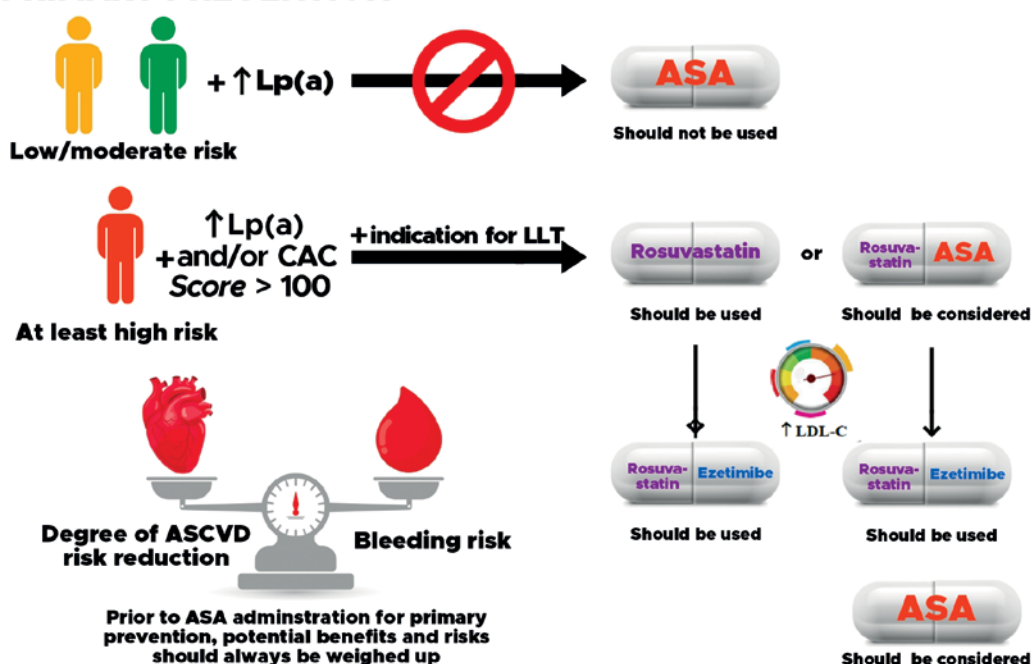
This expert position statement was prepared in connection with a meeting of the Advisory Board

at the invitation of Adamed. Adamed had no influence on the work carried out or on the preparation of the final version of the document, which was the sole result of the expert work of the authors of this document.

Conflict of interest

Maciej Banach has received grant(s)/research support from Amgen, Daiichi-Sankyo, Mylan/Viatris, and Sanofi and has served as a consultant and/or received speaker's fees from Adamed, Amgen, Exceed Pharma, Daiichi-Sankyo, Esperion, Kogen, KRKA, Lilly, MSD, Mylan/Viatris, NewAmsterdam

PRIMARY PREVENTION



SECONDARY PREVENTION

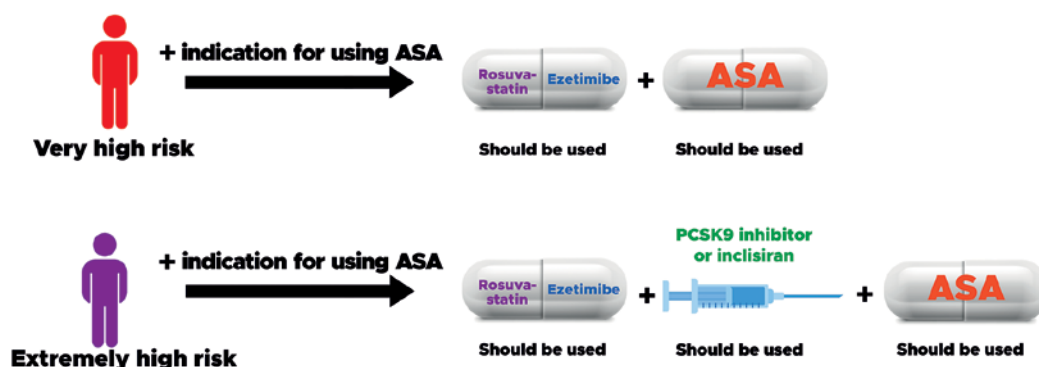


Figure 3. Summary of the Polish Lipid Association (PoLA) recommendations for the use of SPC of rosuvastatin + ASA. *Definitions:* Should be used (Class I), Should be considered (IIa).

ASCVD – atherosclerotic cardiovascular disease, Lp(a) – lipoprotein(a), ASA – acetylsalicylic acid, ASCVD – atherosclerotic cardiovascular disease, CAC – coronary artery calcium, LLT – lipid-lowering therapy, LDL-C – low-density lipoprotein cholesterol, PCSK9 – proprotein convertase subtilisin-kexin type 9, SPC – single pill combination, PPI – proton-pump inhibitor, ESC – European Society of Cardiology.

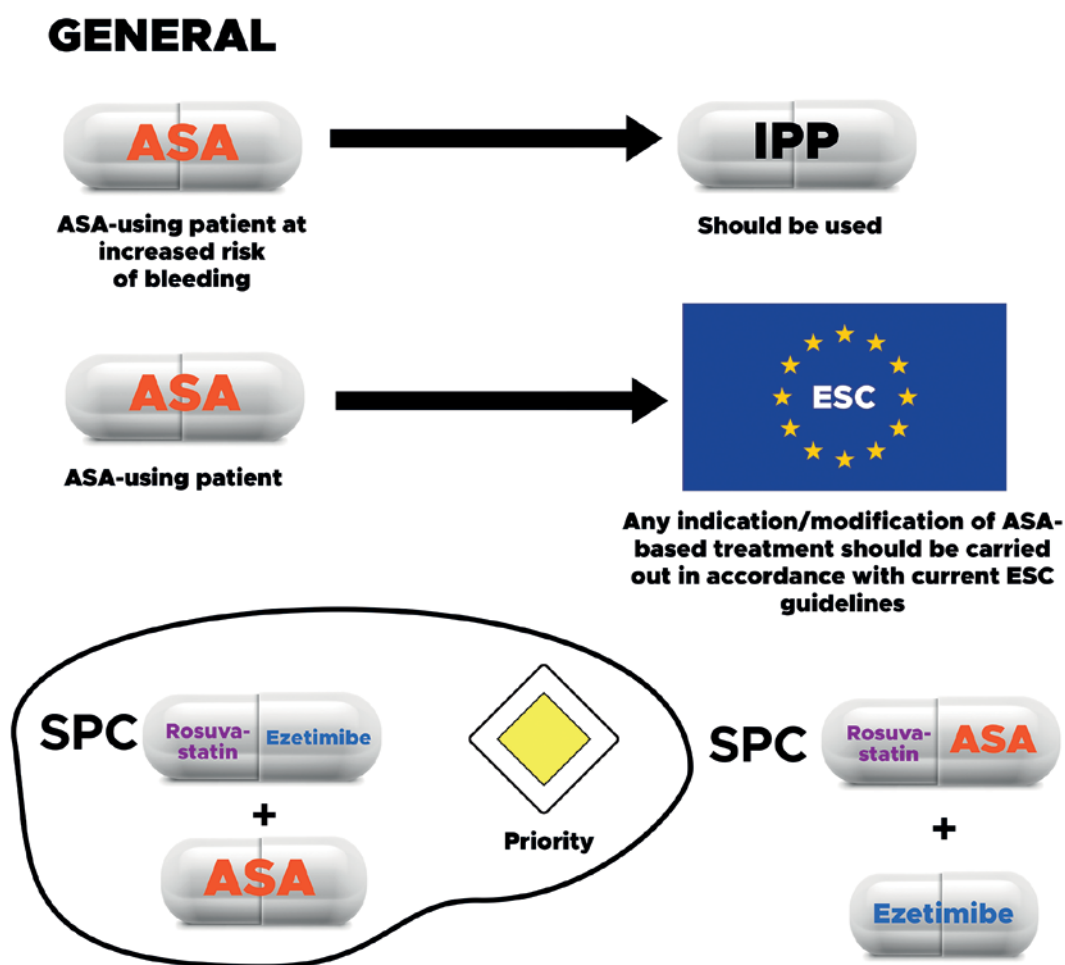


Figure 3. Cont.

Pharma, Novartis, Novo-Nordisk, Polpharma, Sanofi, Teva and Zentiva; Stanisław Surma has received fees from Novartis/Sandoz, KRKA and Pro. Med; Marek Gierlotka: speaker and/or consulting fees from Adamed, Amgen, Astra-Zeneca, Bayer, Berlin-Chemie Menarini, Boehringer Ingelheim, Merck, Novartis, Novo Nordisk, Promed, Sandoz, Sanofi; Piotr Jankowski has received grant(s)/research support and speaker's fees from Adamed, Amgen, KRKA, Novartis, Novo-Nordisk, Polpharma, Sanofi, and Zentiva; Jacek Józwiak: has received speaker and/or consulting fees from Valeant, BIO-RAD, Euroimmun, Adamed, Amgen, Boehringer Ingelheim, Teva, Zentiva, Celgene, Servier, Bioton and ALAB; Jacek Kubica: has received speaker and/or consulting fees from Adamed, AstraZeneca, Boehringer Ingelheim, Ferrer, Gedeon Richter and Servier; Tomasz Tomasik has received fees for consulting and educational services from: Biofarm,

Adamed, Boehringer, Astra Zeneca, Novo-Nordisk and Teva; Robert Gil: speaker and/or consulting fees from: Amgen, Novartis, AstraZeneca, Boehringer Ingelheim, Gedeon Richter, Pfizer, Servier; all other authors do not declare any conflict of interest.

References

1. Roth GA, Mensah GA, Johnson CO, et al.; GBD-NHLBI-JACC Global Burden of Cardiovascular Diseases Writing Group. Global burden of cardiovascular diseases and risk factors, 1990-2019: update from the GBD 2019 study. *J Am Coll Cardiol* 2020; 76: 2982-3021. Erratum in: *J Am Coll Cardiol* 2021; 77: 1958-9.
2. Banach M, Surma S, Toth PP; endorsed by the International Lipid Expert Panel (ILEP). 2023: The year in cardiovascular disease – the year of new and prospective lipid lowering therapies. Can we render dyslipidemia a rare disease by 2024? *Arch Med Sci* 2023; 19: 1602-15.
3. GBD 2019 Risk Factors Collaborators. Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020; 396: 1223-49.
4. Khalid N, Abdullah M, Afzal MA, et al. A systematic analysis of Global Disease Burden of ischemic heart

- disease from 1990-2019. *J Am Coll Cardiol* 2024, 83 (13 Suppl): 1338.
5. Pirillo A, Catapano AL. Inclisiran: how widely and when should we use it? *Curr Atheroscler Rep* 2022; 24: 803-11.
 6. Banach M, Surma S. A look to the past – what has had the biggest impact on lipids in the last four decades? A personal perspective. *Arch Med Sci* 2023; 19: 559-64.
 7. Domanski MJ, Tian X, Wu CO, et al. Time course of LDL cholesterol exposure and cardiovascular disease event risk. *J Am Coll Cardiol* 2020; 76: 1507-16.
 8. Banach M, Surma S. Monitoring of traditional atherosclerosis cardiovascular disease risk factors – is it enough to prevent premature acute coronary syndrome? *Lancet Reg Health Eur* 2024; 38: 100866.
 9. Ray KK, Ference BA, Séverin T, et al. World Heart Federation Cholesterol Roadmap 2022. *Glob Heart* 2022; 17: 75.
 10. Wang N, Woodward M, Huffman MD, Rodgers A. Compounding benefits of cholesterol-lowering therapy for the reduction of major cardiovascular events: systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes* 2022; 15: e008552.
 11. Patti G, Spinoni EG, Grisafi L, Mehran R, Mennuni M. Safety and efficacy of very low LDL-cholesterol intensive lowering: a meta-analysis and meta-regression of randomized trials. *Eur Heart J Cardiovasc Pharmacother* 2023; 9: 138-47.
 12. Yeboyo HG, Aschmann HE, Kaufmann M, Puhan MA. Comparative effectiveness and safety of statins as a class and of specific statins for primary prevention of cardiovascular disease: a systematic review, meta-analysis, and network meta-analysis of randomized trials with 94,283 participants. *Am Heart J* 2019; 210: 18-28.
 13. Ma W, Pan Q, Pan D, Xu T, Zhu H, Li D. Efficacy and safety of lipid-lowering drugs of different intensity on clinical outcomes: a systematic review and network meta-analysis. *Front Pharmacol* 2021; 12: 713007.
 14. Banach M, Burchardt P, Chlebus K, et al. PoLA/CFPIP/PCS/PSLD/PSD/PSH guidelines on diagnosis and therapy of lipid disorders in Poland 2021. *Arch Med Sci* 2021; 17: 1447-547.
 15. Du H, Shi Q, Song P, et al. Global burden attributable to high low-density lipoprotein-cholesterol from 1990 to 2019. *Front Cardiovasc Med* 2022; 9: 903126.
 16. Mensah GA, Fuster V, Murray CJL, Roth GA; Global Burden of Cardiovascular Diseases and Risks Collaborators. Global burden of cardiovascular diseases and risks, 1990-2022. *J Am Coll Cardiol* 2023; 82: 2350-473..
 17. Solnica B, Sygietowicz G, Sitkiewicz D, et al. 2024 Guidelines of the Polish Society of Laboratory Diagnostics and the Polish Lipid Association on laboratory diagnostics of lipid metabolism disorders. *Arch Med Sci* 2024; 20: 357-74.
 18. Mach F, Baigent C, Catapano AL, et al.; ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020; 41: 111-88. Erratum in: *Eur Heart J* 2020; 41: 4255.
 19. Visseren FLJ, Mach F, Smulders YM, et al.; ESC National Cardiac Societies; ESC Scientific Document Group. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2021; 42: 3227-337. Erratum in: *Eur Heart J* 2022; 43: 4468.
 20. Banach M, Penson PE, Vrablik M, et al.; ACS EuroPath Central & South European Countries Project. Optimal use of lipid-lowering therapy after acute coronary syndromes: a position paper endorsed by the International Lipid Expert Panel (ILEP). *Pharmacol Res* 2021; 166: 105499.
 21. Byrne RA, Rossello X, Coughlan JJ, et al.; ESC Scientific Document Group. 2023 ESC Guidelines for the management of acute coronary syndromes. *Eur Heart J* 2023; 44: 3720-826. Erratum in: *Eur Heart J* 2024; 45: 1145.
 22. Banach M, Reiner Ž, Surma S, et al.; International Lipid Expert Panel (ILEP). 2024 Recommendations on the optimal use of lipid-lowering therapy in established atherosclerotic cardiovascular disease and following acute coronary syndromes: a position paper of the International Lipid Expert Panel (ILEP). *Drugs* 2024; 84: 1541-77.
 23. Vrints C, Andreotti F, Koskinas KC, et al.; ESC Scientific Document Group. 2024 ESC Guidelines for the management of chronic coronary syndromes. *Eur Heart J* 2024; 45: 3415-537.
 24. Banach M, Jaiswal V, Ang SP, et al. Impact of lipid-lowering combination therapy with statins and ezetimibe vs statin monotherapy on the reduction of cardiovascular outcomes. A meta-analysis. *Mayo Clin Proc* 2025; doi: 10.1016/j.mayocp.2025.01.018.
 25. Lee SJ, Joo JH, Park S, et al. Combination lipid-lowering therapy in patients undergoing percutaneous coronary intervention. *J Am Coll Cardiol* 2023; 82: 401-10.
 26. Lewek J, Niedziela J, Desperak P, et al. Intensive statin therapy versus upfront combination therapy of statin and ezetimibe in patients with acute coronary syndrome: a propensity score matching analysis based on the PL-ACS Data. *J Am Heart Assoc* 2023; 12: e030414.
 27. Jang JY, Kim S, Cho J, Chun SY, You SC, Kim JS. Comparative effectiveness of moderate-intensity statin with ezetimibe therapy versus high-intensity statin monotherapy in patients with acute coronary syndrome: a nationwide cohort study. *Sci Rep* 2024; 14: 838.
 28. Oliveira G, Balieiro C, Soares Silva AL, et al. Cardiovascular benefits of statin plus ezetimibe combination therapy versus statin monotherapy in acute coronary syndrome: a meta-analysis of randomized controlled trials. *JACC* 2024; 83 (13 Suppl): 1847.
 29. Jun JE, Jeong IK, Ahn KJ, Chung HY, Hwang YC. Combination of low- or moderate-intensity statin and ezetimibe vs. high-intensity statin monotherapy on primary prevention of cardiovascular disease and all-cause death: a propensity-matched nationwide cohort study. *Eur J Prev Cardiol* 2024; 31: 1205-13.
 30. Damarpally N, Sinha T, Maricela Nunez M, et al. Comparison of effectiveness of high dose statin monotherapy with combination of statin and ezetimibe to prevent cardiovascular events in patients with acute coronary syndrome: a systematic review and meta-analysis. *Cureus* 2024; 16: e55922.
 31. Shaya FT, Sing K, Milam R, Husain F, Del Aguila MA, Patel MY. Lipid-lowering efficacy of ezetimibe in patients with atherosclerotic cardiovascular disease: a systematic review and meta-analyses. *Am J Cardiovasc Drugs* 2020; 20: 239-48.
 32. Kelly FA, de Moraes FCA, Lôbo AOM, et al. Safety and efficacy of moderate-intensity statin plus ezetimibe versus high-intensity statin monotherapy in patients with atherosclerotic cardiovascular disease: a meta-analysis. *J Clin Lipidol* 2024 Aug 14;S1933-2874(24)00230-7. doi: 10.1016/j.jacl.2024.07.013.
 33. Crea F, Niccoli G. Ezetimibe and plaque regression: cholesterol lowering or pleiotropic effects? *J Am Coll Cardiol* 2015; 66: 508-10.
 34. Banach M, Surma S, Guzik TJ, et al. Upfront lipid-lowering combination therapy in high cardiovascular risk

- patients: a route to effective atherosclerotic cardiovascular disease prevention. *Cardiovasc Res* 2025; in press.
35. Ray KK, Haq I, Bilitou A, et al.; SANTORINI Study Investigators. Treatment gaps in the implementation of LDL cholesterol control among high- and very high-risk patients in Europe between 2020 and 2021: the multinational observational SANTORINI study. *Lancet Reg Health Eur* 2023; 29: 100624.
 36. Ray KK, Aguiar C, Arca M, et al. Use of combination therapy is associated with improved LDL-cholesterol management: 1-year follow-up results from the European observational SANTORINI study. *Eur J Prev Cardiol* 2024; 31: 1792-803.
 37. Banach M, Surma S, Kapton-Cieślicka A, et al. Position paper of the Polish Expert Group on the use of pitavastatin in the treatment of lipid disorders in Poland endorsed by the Polish Lipid Association. *Arch Med Sci* 2023; 20: 28-42.
 38. Watts GF, Gidding SS, Hegele RA, et al. International Atherosclerosis Society guidance for implementing best practice in the care of familial hypercholesterolaemia. *Nat Rev Cardiol* 2023; 20: 845-69.
 39. Zhang X, Xing L, Jia X, et al. Comparative lipid-lowering/increasing efficacy of 7 statins in patients with dyslipidemia, cardiovascular diseases, or diabetes mellitus: systematic review and network meta-analyses of 50 randomized controlled trials. *Cardiovasc Ther* 2020; 2020: 3987065.
 40. Shakour N, Ruscica M, Hadizadeh F, et al. Statins and C-reactive protein: in silico evidence on direct interaction. *Arch Med Sci* 2020; 16: 1432-9.
 41. Nissen SE, Nicholls SJ, Sipahi I, et al.; ASTEROID Investigators. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. *JAMA* 2006; 295: 1556-65.
 42. Nicholls SJ, Ballantyne CM, Barter PJ, et al. Effect of two intensive statin regimens on progression of coronary disease. *N Engl J Med* 2011; 365: 2078-87.
 43. Kumar A, Shariff M, Doshi R. Impact of rosuvastatin versus atorvastatin on coronary atherosclerotic plaque volume – a systematic review and meta-analysis with trial sequential analysis of randomized control trials. *Eur J Prev Cardiol* 2020; 27: 2138-41.
 44. Hong SJ, Lee YJ, Kang WC, et al.; LODESTAR investigators. Effect of rosuvastatin versus atorvastatin on new-onset diabetes mellitus in patients treated with high-intensity statin therapy for coronary artery disease: a post-hoc analysis from the LODESTAR randomized clinical trial. *Cardiovasc Diabetol* 2024; 23: 287.
 45. Lee SH, Lee YJ, Heo JH, et al. Combination moderate-intensity statin and ezetimibe therapy for elderly patients with atherosclerosis. *J Am Coll Cardiol*. 2023; 81: 1339-49.
 46. Surma S, Lewek J, Penson PE, Banach M. Statin intolerance: an overview for clinicians. In: *Lipoproteins in Diabetes Mellitus. Contemporary Diabetes*. Jenkins AJ, Toth PP (eds.), Springer 2023; 597-635.
 47. Soleimani H, Mousavi A, Shojaei S, et al. Safety and effectiveness of high-intensity statins versus low/moderate-intensity statins plus ezetimibe in patients with atherosclerotic cardiovascular disease for reaching LDL-C goals: a systematic review and meta-analysis. *Clin Cardiol* 2024; 47: e24334.
 48. Surma S, Shapiro MD, Banach M. Breaking new ground in lipid management: Insights from the 2024 American College of Cardiology Scientific Sessions. *Pharmacol Res* 2024; 205: 107246.
 49. Rea F, Savaré L, Corrao G, Mancina G. Adherence to lipid-lowering treatment by single-pill combination of statin and ezetimibe. *Adv Ther* 2021; 38: 5270-85.
 50. Della Bona R, Giubilato S, Palmieri M, et al. Aspirin in primary prevention: looking for those who enjoy it. *J Clin Med* 2024; 13: 4148.
 51. Desai D, Ahmed HM, Michos ED. Preventing cardiovascular disease in patients with diabetes: use of aspirin for primary prevention. *Curr Cardiol Rep* 2015; 17: 566.
 52. Marx N, Federici M, Schütt K, et al.; ESC Scientific Document Group. 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes. *Eur Heart J* 2023; 44: 4043-140. Erratum in: *Eur Heart J* 2023; 44: 5060. Erratum in: *Eur Heart J* 2024; 45: 518.
 53. Mazzolai L, Teixido-Tura G, Lanzi S, et al.; ESC Scientific Document Group. 2024 ESC Guidelines for the management of peripheral arterial and aortic diseases. *Eur Heart J* 2024; 45: 3538-700.
 54. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *Circulation* 2019; 140: e596-646. Erratum in: *Circulation* 2019; 140: e649-50. Erratum in: *Circulation* 2020; 141: e60. Erratum in: *Circulation* 2020; 141: e774.
 55. Doshi A, Gandhi H, Patel KN, Majmundar M, Doshi R. Aspirin for primary prevention in patients with elevated coronary artery calcium score: a systematic review of current evidences. *Am J Cardiol* 2024; 220: 9-15.
 56. Ajufo E, Ayers CR, Vigen R, et al. Value of coronary artery calcium scanning in association with the net benefit of aspirin in primary prevention of atherosclerotic cardiovascular disease. *JAMA Cardiol* 2021; 6: 179-87. Erratum in: *JAMA Cardiol* 2021; 6: 246.
 57. Caldeira D, Alves M, David C, Costa J, Ferreira JJ, Pinto FJ. Aspirin in the primary prevention of cardiovascular disease on diabetic patients: systematic review and meta-analysis. *Prim Care Diabetes* 2020; 14: 213-21.
 58. ASCEND Study Collaborative Group; Bowman L, Mafham M, Wallendszus K, et al. Effects of aspirin for primary prevention in persons with diabetes mellitus. *N Engl J Med* 2018; 379: 1529-39.
 59. Ma H, Gu Q, Niu H, Li X, Wang R. Benefits and risks associated with aspirin use in patients with diabetes for the primary prevention of cardiovascular events and mortality: a meta-analysis. *Front Endocrinol* 2021; 12: 741374.
 60. Wang M, Yu H, Li Z, Gong D, Liu X. Benefits and risks associated with low-dose aspirin use for the primary prevention of cardiovascular disease: a systematic review and meta-analysis of randomized control trials and trial sequential analysis. *Am J Cardiovasc Drugs* 2022; 22: 657-75.
 61. Masson W, Barbagelata L, Lavalle-Cobo A, et al. Low-doses aspirin in the primary prevention of cardiovascular disease in patients with diabetes: meta-analysis stratified by baseline cardiovascular risk. *Diabetes Metab Syndr* 2022; 16: 102391.
 62. Liu T, Zuo R, Wang J, et al. Cardiovascular disease preventive effects of aspirin combined with different statins in the United States general population. *Sci Rep* 2023; 13: 4585.
 63. Zhou Z, Webb K, Nelson M, et al. Short- and long-term impact of aspirin cessation in older adults: a target trial emulation. *Circulation* 2024; 150 Suppl. 1: 4139675.
 64. Lawler PR, Bhatt DL, Godoy LC, et al. Targeting cardio-

- vascular inflammation: next steps in clinical translation. *Eur Heart J* 2021; 42: 113-31.
65. Makover ME, Surma S, Banach M, Toth PP. Eliminating atherosclerotic cardiovascular disease residual risk. *Eur Heart J* 2023; 44: 4731-3.
 66. Dyrbuś K, Mędrala Z, Konsek K, et al. Lipoprotein(a) and its impact on cardiovascular disease – the Polish perspective: design and first results of the Zabrze-Lipoprotein(a) Registry. *Arch Med Sci* 2024; 20: 1069-76.
 67. Bhatia HS, Trainor P, Carlisle S, et al. Aspirin and cardiovascular risk in individuals with elevated lipoprotein(a): the multi-ethnic study of atherosclerosis. *J Am Heart Assoc* 2024; 13: e033562.
 68. Razavi AC, Richardson LC, Coronado F, et al. Aspirin use for primary prevention among US adults with and without elevated lipoprotein(a). *Am J Prev Cardiol* 2024; 18: 100674.
 69. Surma S, Sosnowska B, Reiner Ž, Banach M. New data allow to better understand the secrets of lipoprotein(a): is that for sure? *Eur Heart J Open* 2024; 4: oea066.
 70. Burzyńska M, Jankowski P, Babicki M, Banach M, Chudzik M. Prevalence of hyperlipoproteinemia(a) in individuals of European ancestry treated at outpatient cardiology clinics: results from a cross-sectional STAR-Lp(a) study. *Pol Arch Intern Med* 2024; 134: 16860.
 71. Sosnowska B, Stepinska J, Mitkowski P, et al. Recommendations of the Experts of the Polish Cardiac Society (PCS) and the Polish Lipid Association (PoLA) on the diagnosis and management of elevated lipoprotein(a) levels. *Arch Med Sci* 2024; 20: 8-27.
 72. Surma S, Zembala MO, Okopień B, Banach M. Lipoprotein (a) and lipid-lowering treatment from the perspective of a cardiac surgeon. An impact on the prognosis in patients with aortic valve replacement and after heart transplantation. *Int J Cardiol Cardiovasc Risk Prev* 2024; 22: 200297.
 73. Sosnowska B, Surma S, Banach M. Targeted treatment against lipoprotein (a): the coming breakthrough in lipid lowering therapy. *Pharmaceuticals (Basel)* 2022; 15: 1573.
 74. Abrignani MG, Lombardo A, Braschi A, Renda N, Abrignani V. Proton pump inhibitors and gastroprotection in patients treated with antithrombotic drugs: a cardiologic point of view. *World J Cardiol* 2023; 15: 375-94.