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Acetylsalicylic acid in 2019: known benefits and new challenges

Kwas acetylosalicylowy AD 2019 — znane zalety, nowe wyzwania

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Abstract

In this paper, we present a full review of the present guidelines on antiplatelet properties and indications for the prophylactic usage of acetylsalicylic acid (ASA). We include the results of the latest research mainly on primary prevention, the optimal dosage in the context of ASA resistance, and the possibilities of long-term co-operation with patients requiring ASA administration. We also discuss prevention methods of frequently occurring gastrointestinal symptoms of drug intolerance.

Key words: ASA, atherosclerosis, pharmacotherapy, ischaemic heart disease, safety profile

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History of medical uses of acetylsalicylic acid

Drugs that belong to salicylates are as old as medicine. The analgesic, antipyretic and anti-inflammatory properties of willow bark were already known in distant antiquity: the oldest references appear on Sumerian stone tablets from around 2000 B.C. The Ebers Papyrus (around 1550 B.C.) is another proof that the benefits of salicylates were understood. Similarly, most of those sometimes referred to as the 'Fathers of Medicine' recommended the use of willow extract for medicinal purposes, including Hippocrates, Celsus, Pedanios Dioskurydes, Pliny the Elder, and Galen. The status quo did not change much until the 18th century, when Reverend Edward Stone described the unusual effects of willow bark in the treatment of fever associated with malaria symptoms, comparing it to the applied Jesuit bark (it is now known that it was rich in quinine). He presented the results of his research in 1763 to a meeting of the Royal Society, which led to plants rich in salicylates becoming a cheaper substitute for antimalarial preparations.

The nineteenth century brought identification of the active substance found in willow bark: in 1828, Joseph Buchner isolated salicin crystals. Ten years later, Raffaele Piria discovered a method of even more effective salicylic acid extraction. The following years brought increasing knowledge about the characteristics of salicylates usage, and also about their side effects, with gastric irritation to the fore. In 1897, Felix Hoffman was inspired by the side effects of sodium salicylate experienced by his father who had been prescribed it as part of rheumatism treatment. Hoffman developed an efficient method of producing its derivative, acetylsalicylic acid (ASA), which after acetylation gained valuable properties of heart disease prevention, as is known nowadays. Initial studies were difficult because of suspected heart damage. Finally, the drug patent was

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granted to Bayer, and since 1899 ASA has been available under the trade name Aspirin®, which was later recognised as the equivalent of the chemical name.

The first reports of the potential impact of ASA on the cardiovascular system in the form of a reduced number of cardiovascular incidents did not appear until 1950. A breakthrough discovery in this regard was made by an American doctor, Lawrence L. Craven, who observed an increased risk of bleeding in patients taking ASA as a painkiller and hypothesised that it was an anticoagulant and may lower the risk of coronary thrombosis and heart attack. His observational studies, however, did not gain widespread acceptance, and incidentally Dr Craven himself died of a heart attack. It was not until the 1980s that the world of medicine accepted the effectiveness of ASA in counteracting arterial thromboembolic events: in 1988, the American Food and Drug Administration (FDA) recognised secondary prevention of myocardial infarction as an indication for ASA.

Mechanism of action and dosage of ASA

Acetylsalicylic acid is a non-steroidal anti-inflammatory drug (NSAID), showing anti-inflammatory, antipyretic, analgesic and antiaggregatory effects. The basic mechanism of action is acetylation of the hydroxyl group of serine located in the active site of cyclooxygenase (COX, cyclooxygenase), which leads to irreversible inactivation of the enzyme by preventing its association with arachidonic acid. Cyclooxygenase occurs in two forms: COX-1, present mainly in platelets, is largely responsible for the production of thromboxane, while COX-2 (common in nucleated cells, including endothelium) is largely responsible for the production of anticoagulant and pro-inflammatory prostaglandins. The ability of ASA to acetylate serine in both COX-1 and COX-2 is the explanation of its broad spectrum of activity. A lack of COX activity significantly reduces the number of emerging intra- and extracellular mediators, which include prostaglandins, prostacyclins and thromboxanes. Reducing the formation of prostanoids suppresses inflammation, and thromboxane inhibits platelet aggregation, making it difficult to form clots.

Importantly, ASA inhibits COX-1 almost 200 times more strongly than it does COX-2. This means that the expected anti-platelet effect can be achieved with a much lower dose than is necessary to achieve the anti-inflammatory effect. This reduces the risk of side effects (dose-dependent) and allows a patient to take small, anti-platelet doses over a long period.

ASA has an antiplatelet effect already at doses of about 50 mg (in the case of chronic use even as little as 20 mg), but higher doses cause a more predictable and faster response (in healthy people, after taking an 80 mg dose the full effect takes 15–30 minutes). This justifies their use, for example, as the first dose in a heart attack. Restoration of the thrombotic potential of platelets is therefore possible by renewing the thrombocyte population (living for about 10 days) not affected by ASA.

Views on the correct dose of ASA as an antiplatelet drug remain surprisingly diverse. In most European countries, including Germany, Austria, France, Spain, Belgium and Portugal, the usual dose is 100 mg/day. In the United States, the most preferred dose is 81 mg, while stressing that the 75 mg/day dose seems too low for an adult. In Australia, the dose range is from 75 up to 150 mg, however the most commonly chosen is 100 mg/day. The most commonly prescribed dose in Poland, 75 mg/day, is equally often used in principle only in Great Britain. Although doses from 75 mg/day are usually mentioned as antiplatelet agents, a 100 mg ASA tablet appears on the list of 'essential medicines' published by the World Health Organisation (WHO) [1].

An attempt to resolve dosage controversies have resulted in a systematic review and meta-analysis that compared 11 randomised trials involving a total of 104,101 patients with a median follow-up of 60 months [2]. The range of doses tested was significant: from 50 mg/day to as much as 990 mg/day, but no significant strong differentiation of the preventive effect was found depending on the dose. Subtle trends were noted when broken down into doses: 100 mg/day (better indicators regarding the risk of death, cancer death, cancer and major gastrointestinal bleeding); over 100 mg/day (stronger cardiovascular protection); no more than 100 mg/day (better tolerance, lower risk of intracranial bleeding). Therefore, it seems sensible to consider that in order to provide full protection, the dose should be maximised, while avoiding an ineffective increase above the 100 mg/day threshold. In a recent meta-analysis, insufficient preventive efficacy of the lowest doses in patients with higher (> 70–80 kg) body weight was suggested [3]. This is in line with analysis of the authors of this paper regarding of risk factors for ASA resistance (see below). An increased rate of thrombocyte renewal is observed in diabetes mellitus; data suggests a greater efficacy of ASA administered twice a day.

Indications for use of ASA according to current guidelines

ASA has revolutionised modern medicine to a degree comparable to penicillin, becoming one of the most important drugs of the 20th century. Its primary use is secondary prevention of cardiovascular diseases *i.e.* thrombotic complications of atherosclerosis. The effect of ASA on venous thrombosis (reduction of relapses by more than 25%; ASPIRE study) or intracardiac (in atrial fibrillation) is weaker than that of drugs that inhibit the plasma system. A separate issue, and the subject of some controversy, is

Table 1. A shift in risk of major clinical events during chronic use of acetylsalicylic acid (ASA) — Antithrombotic Triallists Collaboration 2009 meta-analysis (modified based on [5])

Clinical event	Absolute annual risk difference when using ASA vs. placebo (Δ%/year)	
	Primary prevention (n = 660,000 patients × years)	Secondary prevention (n = 43,000 patients × years)
Serious coronary event	–0.06	–1.00
Non-fatal heart attack	–0.05	–0.66
Death from coronary event	–0.01	–0.34
Stroke	–0.01	–0.46
Haemorrhagic stroke	–0.01	Data difficult to compile
Death from cardiovascular reasons	–0.01	–0.29
Cardiovascular event	–0.07	–1.49
Serious extracranial haemorrhage	+0.03	Data difficult to compile

the preventive effect of ASA on the formation of cancers, especially of the large intestine.

The 2016 guidelines of the European Society of Cardiology (ESC) on the prevention of cardiovascular diseases [4] clearly highlight the key role of ASA in the treatment of patients as part of secondary prevention, with clinically confirmed coronary artery disease, history of ischaemic or symptomatic stroke, and atherosclerosis of peripheral arteries. The starting point was the prospective, blinded SAPAT (Swedish Angina Pectoris Aspirin Trial) study, which demonstrated a 34% reduction in the risk of a complex endpoint (in the form of sudden cardiac death or heart attack in patients), included in subsequent editions of the ESC guidelines on the treatment of stable coronary heart disease.

In a later meta-analysis of Antiplatelet Triallists' Collaboration (17,000 patients, Table 1), it was demonstrated that patients with high cardiovascular risk receiving ASA showed a 25% reduction in the risk of cardiovascular events (from 8.2% to 6.7% per year). The risk of stroke was reduced from 2.6% per year to 2.1% per year, and the risk of coronary complications from 5.3% per year to 4.3% per year [5]. Despite a simultaneous increase in the risk of significant bleeding, a reduction in overall mortality of 10% was confirmed. These guidelines explicitly recommend the use of ASA after acute coronary syndrome and ischaemic stroke or transient ischaemic episode, with the highest class of IA recommendations, permanently. In many situations, ASA is part of double or triple anticoagulant therapy, most often used in recent acute coronary syndrome or arterial stent surgery. This vast area of medicine goes beyond the scope of this study, but is discussed in detail in the recently developed ESC Expert Document [6].

A further recommendation to use ASA in patients with known ischaemic heart disease after a stroke or transient ischaemic attack (TIA) and with symptomatic peripheral vascular disease, are the American Heart Association/ /American College of Cardiology Foundation (AHA/ACCF) 2011 guidelines regarding secondary prevention and risk--reducing therapies in patients with coronary artery disease and other atherosclerotic vascular disease. These state that in patients with any type of coronary artery disease, especially after a heart attack, or in patients who have had cerebrovascular incidents and have no contraindications, chronic ASA therapy at a dose of 75–162 mg/day should be initiated and continued.

However, there are serious doubts regarding primary prevention. The systematic review cited in the European document, covering six studies including a total of 95,000 patients without overt cardiovascular and cerebrovascular disease using chronic ASA versus placebo did not produce any revelations. Reducing the risk of cardiovascular complications from 0.57% per year to 0.51% per year with a simultaneous increase in the risk of major extracranial and gastrointestinal bleeding by 0.03% per year, and no change in the risk of cardiovascular mortality, constitute the basis for a contraindication to the chronic use of ASA in people without atherosclerosis and people with low cardiovascular risk (class IIIB). These findings were confirmed in the latest, even more extensive, meta-analysis (157,248 patients): again, ASA used in primary prevention was proved to reduce the risk of heart attack by 18%, with no effect on total mortality at an average follow-up of 6.6 years, due to an increase in the frequency of clinically significant bleeding by 47% (intracranial — 33%) [7].

A slightly different position was presented by the authors of the US Prevention Service Task Force guidelines [8] regarding the use of ASA in primary prevention, in opposition to European guidelines. The US document admits two groups of patients for whom ASA is to be considered, including one group in which it is in fact recommended. These are people who meet the following criteria: age

50–59 years who have a low risk of bleeding, an expected survival of at least 10 years, an expected duration of taking ASA of not less than 10 years, and a cardiovascular risk calculated using ASCVD (Atherosclerotic Cardiovascular Disease) of not lower than 10%. They are recommended to use ASA in a dose of 75–150 mg/day. For people who meet the other criteria, but who are a decade older (60–69 years), the inclusion of ASA may be considered according to the US guidelines. The effects of such proceedings in a group of 10,000 patients would be to prevent 225 heart attacks, 84 ischaemic strokes and 139 bowel cancers, but at the expense of 284 serious extracranial bleedings and 23 haemorrhagic strokes.

Given the results of the latest ASCEND (A Study of Cardiovascular Events iN Diabetes) [9] and ARRIVE [10] studies published during the ESC 2018 Congress in Munich, the issue of primary prevention recommendations is becoming even more distant. The ARRIVE study was designed to study the effect of taking 100 mg/day ASA compared to placebo in a group of 12,500 patients with intermediate cardiovascular risk (defined as 10–20% in 10 years; actual risk was approximately 8.5% in 10 years) but no diabetes or known cardiovascular disease. Male patients had to be at least 55 years old and had to have two additional risk factors, women had to be at least 60 years-old and to have three risk factors. The use of ASA was not found to significantly change the risk of cardiovascular events, while the risk of gastrointestinal bleeding is significantly increased (from 0.5% to 1%/year); severe bleeding occurred in only two patients in the placebo group and in four in the ASA group. The disadvantages of the study include an underestimation of the level of cardiovascular risk, as well as problems with the co-operation of patients during the trial patients who have taken at least 60% of doses correctly have been shown to have a 47% reduction in the risk of heart attack typical of other studies using ASA.

The impact of taking 100 mg/day of ASA for more than seven years compared to taking placebo in a group of nearly 15,500 was analysed in the ASCEND study [7] with known diabetes but no known cardiovascular disease. A statistically significant reduction in the risk of cardiovascular events by as much as 12% was overshadowed by the fact that the risk of major bleeding (usually from the gastrointestinal tract) increased by as much as 29%. The potential beneficial preventive effect was therefore almost completely counteracted by the side effects.

Similarly, the identification of candidates for ASA as part of primary prevention based on age did not meet expectations — the ASPREE study (ASPirin in the Prevention of Events in the Elderly) [11] conducted in a population of fit seniors (median 74 years) focused on reducing the risk of death, dementia or permanent disability. Protective features were not reported, although an expected 38% increase in the incidence of haemorrhagic incidents was.

In summary, optimal strategies for the prophylactic use of ASA end up with an accurate identification of populations in which the reduction of the risk of thrombotic complications connected to atherosclerosis (ASA's protective effect on myocardial infarction is indisputable) exceeds the relatively constant values of excessive, dangerous bleeding. Current data indicates only the group of secondary prevention (after a heart attack or stroke) as having clear benefits from preventive ASA therapy.

Resistance to ASA — failure to prevent (im)possible to overcome?

Another important element of ASA pharmacotherapy is the phenomenon of resistance, in other words failure to achieve an adequate clinical or pharmacological response to typical doses of the drug. The phenomenon of resistance has been known since the mid-1990s when [12] when loss of full response to treatment was reported in up to a third of patients, while after increasing the dose to 1.3 g/day resistance remained in 8% of patients. The basic problem remains to define whether resistance is actually increasing, or whether there is an individual non-response to ASA a priori.

Gum et al. [13], in a study published in 2006, decided to verify the prognostic consequences of ASA resistance. Aspirin resistance was found in 5.2% of 326 patients with stable cardiovascular disease receiving ASA at 325 mg/day. The risk of a composite endpoint was 3.12 times higher in the population resistant to ASA over a 2-year follow-up period. Therefore, this phenomenon is clinically significant. In a population of patients with coronary artery disease qualified for revascularisation in our own clinic, the frequency of incorrect response to ASA was about 13% [14]. The study examined whether the dose increase would ensure adequate platelet response, and attempted to identify predictors of ASA resistance. In the Lodz study, the main risk factors for resistance were male sex, high platelet count, and leucocytosis. In view of breaking the resistance in 62.5% of patients after doubling the dose to 150 mg/day (more often in men and in patients with moderately exceeded platelet function indices), it seems reasonable to personalise the dose in relation to specific conditions in individual patients, and the dose of 75 mg/day in the entire Polish population cannot be considered sufficient. The authors of the German BOCLA-Plan (the BOchum CLopidogrel and Aspirin Plan) study [15] proved that in a group of 504 patients treated with ASA, 80.6% of patients responded to the 100 mg/day dose, while the remaining 19.4% of patients responded to higher doses: 18.35% responded to a 300 mg/day dose, and 1.05% responded to a 500 mg/day dose. Importantly, no definitive resistance was found at all.

This confirms the validity of dose escalation in patients at high risk for atherosclerosis. In the BOCLA study, the risk factors were a history of acute coronary syndrome, elevated troponin levels, diabetes, high platelet counts, elevated C-reactive protein (CRP), glycated haemoglobin (HbA_{1c}), creatinine and haemoglobin, and proven poor response to clopidogrel.

The BOCLA study sheds new light on the problem of resistance; its results suggest that individual non-response to ASA is not a common cause. It seems that, as in the case of other preventive therapies, an important reason may be a failure to comply with medical instructions by a significant group of patients. Even under supervised clinical trials, as many as 40% of patients are found not to be taking the drug as prescribed after several years.

Improving patient co-operation in the field of preventive therapies

Prevention of cardiovascular incidents can only be truly effective when it is uninterrupted. Differences in the perception of the benefits and losses of treatment may occur at the professional level — EUROASPIRE registers IV and V indicate that 7% of patients with coronary artery disease do not take ASA, and surely the patient's perspective on treatment neccessity differs from the doctor's assessment.

The problem is not just ASA; it is estimated that insufficient therapeutic compliance is responsible for approximately 10% of acute circulatory complications in Europe [16]. Quite often, discontinuation of ASA therapy may also have an iatrogenic background, and one of the main causes is gastrointestinal side effects. These are much more often of a dyspeptic nature, rather than major bleeding. The European guidelines for the prevention of cardiovascular diseases explicitly recommend maximum simplification of treatment with active surveillance measures, assessing the level of patient co-operation, and identifying failures; it is also recommended to use tablets containing more than one active ingredient.

Risk factors for the significant problem of insufficient persistence in the use of preventive therapies seem to be indications for treatment that do not cause subjective discomfort, as well as excessive complexity of therapy causing adverse effects. An online survey published in 2011 found that out of 1,007 respondents, among whom 67% took 81 mg of ASA, as many as 88% felt heartburn or reflux, 15% missed doses due to combinations with other drugs or just gastro-oesophageal problems, and as many as 19% made interruptions in therapy due to dyspeptic symptoms [17]. This resulted in the insufficient co-operation of 28% of respondents.

Tolerance for chronic ASA treatment varies from person to person, but some side effects are quite common. In CAPRIE (Clopidogrel vs. Aspirin in Patients at Risk of Ischaemic Events), ASA at a dose of 325 mg/day caused gastrointestinal bleeding in 2.7% of patients, gastrointestinal ulceration in 1.2%, and indigestion, nausea or vomiting in up to 17.6%. Ulcers and bleeding after ASA are mainly caused by inhibition of prostaglandin's protective effect on the gastric mucosa, but also by a decrease in gastrointestinal pH and, of course, antiplatelet effect (Figure 1).

One way to improve ASA tolerance is to modify the tablet form, and enteric-coated tablets are commonly used. These improve the tolerance of the therapy but they are not a complete solution as they protect primarily the stomach, but not the intestine. Gastro-resistant tablets compared to buffered tablets are associated with a greater need for proton pump inhibitors (PPIs) or H_2 antagonists (14.4% vs. 25.4%). Buffered tablets were also characterised by a 39% lower number of ulcers and a 21% reduction of blood in the stool after 12 months of therapy — this form of galling is not widely available.

From the perspective of gastrointestinal complications, the preventive use of PPI also seems beneficial. In American and Polish guidelines, it is recommended that patients with indications for antiplatelet therapy have their gastrointestinal risk assessed. This is elevated in patients with a history of complicated or non-complicated peptic ulcer disease (in this group of patients it is recommended to eradicate Helicobacter pylori in case of confirmed status of the carrier), a history of gastrointestinal bleeding during dual antiplatelet therapy, as well as those treated with oral anticoagulants (OAC). PPI should be included in the high-risk group. Patients who do not meet the above-mentioned criteria should also be evaluated for the following risk factors: age 60 and over, corticosteroid therapy, dyspepsia, or gastrointestinal reflux symptoms. In these patients, the inclusion of PPI also seems to be the optimal solution. It has been estimated that a combination of ASA and PPI reduces the risk of gastrointestinal bleeding over a lifetime from 7.2% to 3.4%, increases the adherence rate from 71% to 74%, reduces the incidence of recurrent heart attack by 26,100 patients, extends life by an average of 38 days, and reduces the total cost of treating patients by $19,000 over a year. Unfortunately, PPI does not show an additive effect on ASA, and its protective effect is limited only to the stomach. In addition, therapeutic compliance with PPI is also not ideal. However, the coatings of the gastro-resistant tablets may affect the effectiveness of the medicine. An important observation concerns the identification of pseudo-resistant patients due to the type of gastro-resistant tablet used so far. Among type 2 diabetic patients using ASA 325 mg/day, the percentage of people whose thromboxane activity remained dangerously high was the highest in the group of enteric-coated tablets (52.8%) compared to the group receiving lipid tablets (8.1%) or ordinary tablets (15.8%) [18]. Other studies have provided evidence of the effect of enteric coating on the bioavailability of ASA and

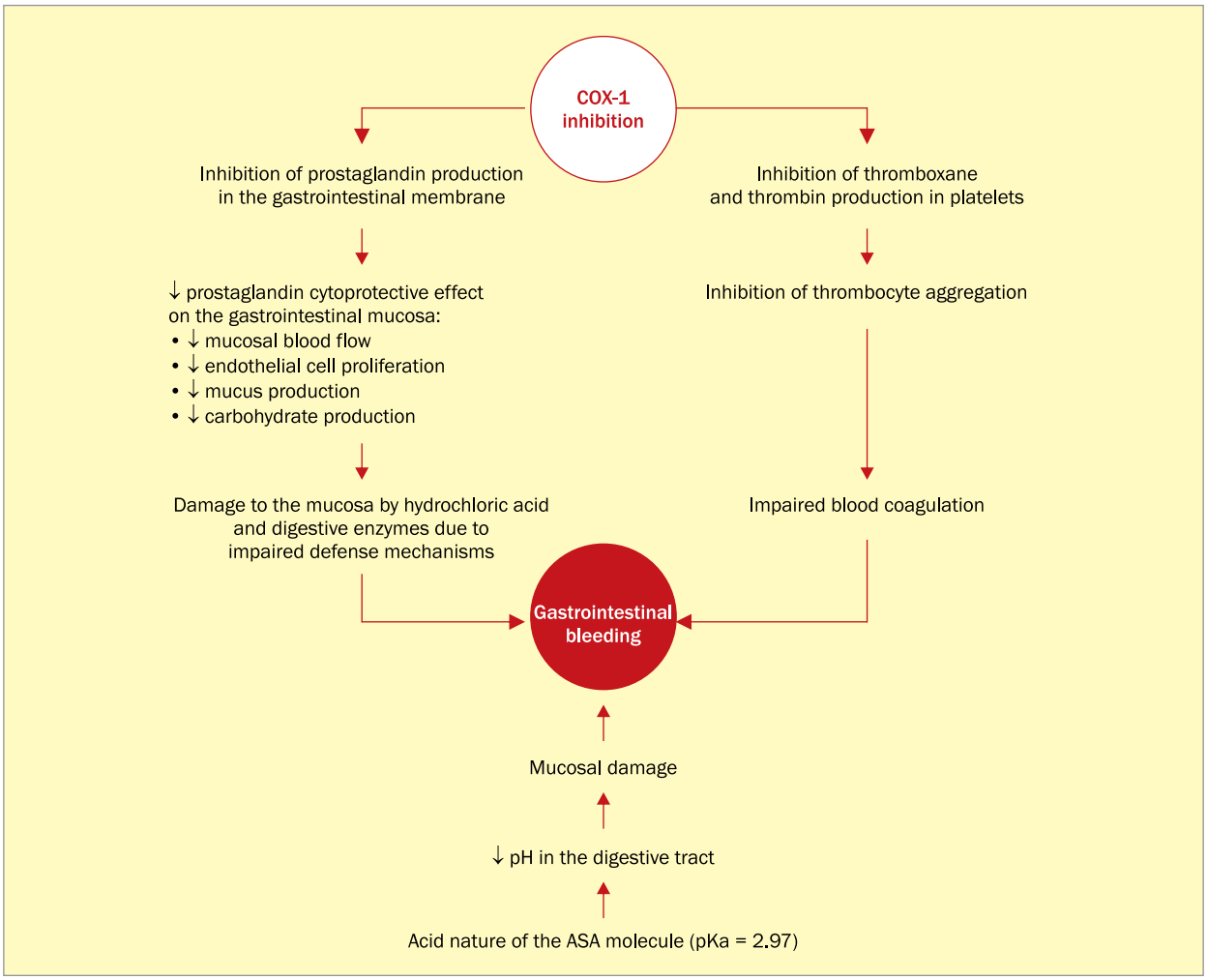

Figure 1. Inhibition of cyclooxygenase 1 (COX-1) by acetylsalicylic acid (ASA) and gastrointestinal adverse reactions

its significant negative role in limiting the preventive effect of the drug [19].

Recently, combinations of ASA and glycine have also appeared (tablet buffered on the Polish market containing 100 mg ASA with 40 mg glycine). The combination of ASA with glycine results from the fact that it is of key importance in the lining of the gastrointestinal tract formation, as it is significantly involved in the synthesis of collagen and gelatin. In addition, it has anti-inflammatory, cytoprotective and immunomodulatory properties. It reduces tissue ischaemia caused by haemorrhagic shock, stimulates protein synthesis in the cells of the gastrointestinal tract, and protects them from oxidative stress. Animal studies have also found its vasodilatory effect and effect on gastric acid secretion, as well as on the thickness of the walls and mucous membrane of the gastrointestinal tract. Overall, it protects against stress ulcers.

It also turns out that this amino acid increases the solubility of ASA and facilitates its absorption, prevents the irritating effect on the mucosa and supports the regeneration of the digestive tract. In 2014, Murtaza et al. [20] conducted studies on increasing the solubility and absorption of ASA in assistance of various amino acids. The results were promising, as significantly higher solubility was observed for most of the tested amino acids. The authors suggested that administration of ASA with free amino acids or protein meals may significantly affect drug absorption. Müller et al. [21] compared the effect of 500 mg ASA and the same dose of ASA with 250 mg glycine on gastric and duodenal mucosa in 20 healthy volunteers during four weeks of therapy. Nine out of 10 patients reported distressing dyspeptic symptoms in the group receiving ASA only, while none did in the group treated with glycine. There is also clinical evidence to improve the tolerance of ASA administered with glycine: Kusche et al. [22] sequentially compared the observations of patients undergoing long-term ASA therapy at a dose of 50–100 mg/day to the subsequent inclusion

of combination therapy with ASA and glycine after a monotherapy period of at least one month. Tolerance was assessed on the basis of an interview and compared to previous observations of the subjects.

It turned out that the percentage of patients without gastrointestinal symptoms increased from 28.2% to 60.6%. The percentage of patients with recurrent stomach discomfort during therapy decreased from 8.5% to 0.5%. Based on these results, it was concluded that the addition of glycine to standard therapy not only increases the bioavailability of ASA, allowing the patient to benefit fully from the administered dose, but also at the same time it significantly improves ASA tolerance by reducing its gastrointestinal adverse effects. Such management also allows for potential reduction or withdrawal from PPI therapy, thanks to which their various adverse effects can be avoided.

Conclusions

ASA does not lose its relevance as primary therapy in the secondary prevention of cardiovascular complications and strokes. According to the current consensus in Europe is not recommended for primary prevention because of the increased risk of haemorrhagic complications. The clinical effectiveness of the drug is influenced by its tolerance profile, with dominant uncomfortable symptoms of gastrointestinal mucosal irritation. Some patients may need PPI administration. In addition to widely used, but not fully enteric, neutral forms of the drug, a new proposal to solve the problem of intolerance is a tablet containing a combination of ASA in a dose of 100 mg and 40 mg of glycine. This is an interesting alternative, improving the tolerance profile of the drug on the part of the gastrointestinal tract without increasing costs and the number of tablets taken, which may translate into better therapeutic compliance, and therefore better long-term effects in preventing serious cardiovascular incidents.

Conflict of interest

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Streszczenie

W niniejszym opracowaniu podsumowano aktualne zalecenia dotyczące właściwości przeciwpłytkowych oraz wskazań do profilaktycznego stosowania małych dawek kwasu acetylosalicylowego (ASA). Omówiono wyniki najnowszych badań dotyczących przede wszystkim prewencji pierwotnej, optymalnego dawkowania w kontekście zagadnienia aspirynooporności oraz możliwości poprawy długoterminowej współpracy pacjentów wymagających stosowania ASA. Omówiono również sposoby zapobiegania stosunkowo częstemu problemowi nietolerancji leku ze strony przewodu pokarmowego.

Słowa kluczowe: ASA, miażdżyca, farmakoterapia, choroba niedokrwienna, bezpieczeństwo

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