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Antiplatelet treatment in the primary prophylaxis of cardiovascular disease in patients with arterial hypertension

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Abstract

The benefits of using acetylsalicylic acid (ASA) in the primary prophylaxis of cardiovascular diseases may only slightly exceed the risk of serious bleeding. This warrants the search for alternative, safer preparations with antiaggregatory properties, which could be used in patients burdened with cardiovascular risk factors. Antiaggregatory compounds identified in water-soluble tomato extract include nucleosides, flavonoids, and phenolic acids. The action of standardized tomato extract is multidirectional, reversible, and weaker in comparison to ASA. The European Food Safety Authority (EFSA) has approved this preparation as a dietary agent with antiaggregatory properties. The use of standardized tomato extract appears beneficial in arterial hypertension patients with low or moderate cardiovascular risk and in patients in whom good pressure control cannot be achieved.

Key words: acetylsalicylic acid, standardized tomato extract.

Streszczenie

Korzyści ze stosowania kwasu acetylosalicylowego (ASA) w profilaktyce pierwotnej chorób sercowo-naczyniowych mogą w niewielkim stopniu przewyższać ryzyko poważnych krwawień. Dlatego zasadne jest poszukiwanie alternatywnych do ASA, bezpiecznych preparatów o właściwościach antyagregacyjnych, które będą mogły być stosowane u osób, u których występują czynniki ryzyka chorób sercowo-naczyniowych. Do związków o właściwościach antyagregacyjnych, które zostały zidentyfikowane w rozpuszczalnym w wodzie ekstrakcie z pomidora, należą: nukleozydy, flawonoidy i kwasy fenolowe. Działanie standaryzowanego ekstraktu z pomidorów jest wielokierunkowe, odwracalne i słabsze w porównaniu z ASA. Europejska Agencja ds. Bezpieczeństwa Żywności zaakceptowała ten preparat jako środek dietetyczny o właściwościach antyagregacyjnych. Wydaje się, że zastosowanie standaryzowanego ekstraktu z pomidorów u pacjentów chorujących na nadciśnienie tętnicze z grup niskiego i umiarkowanego ryzyka sercowo-naczyniowego oraz u pacjentów nieosiągających dobrej kontroli ciśnienia jest korzystne.

Słowa kluczowe: kwas acetylosalicylowy, standaryzowany ekstrakt z pomidorów.

Acetylsalicylic acid in the primary prophylaxis of cardiovascular disease

Acetylsalicylic acid (ASA) belongs to the group of nonsteroidal anti-inflammatory drugs which irreversibly inhibit prostaglandin cyclooxygenases by acetylating serine located at the binding site of arachidonic acid [1]. Acetylsalicylic acid blocks the cyclooxygenase enzyme center for arachidonic acid, consequently inhibiting the production of prostanoids: thromboxane A2 (TXA2), prostaglandins, and prostacyclins. The antiplatelet effect of ASA consists in inhibiting the production of TXA2, which activates blood platelets, increases aggregation, and narrows the blood vessels. Considering the fact that blood platelets have no cellular nuclei, preventing them from synthesizing cyclooxygenase, the antiaggregatory action of ASA is irreversible; in other words, it persists until a new generation of platelets is produced. This determines the duration of aspirin's antiaggregatory action, which lasts for approx. 10 days [2]. The most common adverse effects of ASA are: heartburn, gastric ailments, and microischemias of the gastric mucosa resulting from the inhibition of prostaglandin E2 (PGE2) production. Chronic ASA use is associated with rare or very rare occurrence of severe adverse effects that can be life-threatening. These consist in serious bleeding,

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such as gastrointestinal tract bleeding or cerebral bleeding (especially in patients with uncontrolled hypertension and/or receiving antithrombotic agents) [3]. Some patients develop high on-treatment platelet reactivity (HTPR), i.e., re-sistance to antiplatelet treatment. Aspirin resistance is a common clinical problem; various clinical studies estimate its prevalence at 2–57% [4]. The results obtained by a study using the VerifyNow Aspirin test appear credible; the authors analyzed 468 patients with stable ischemic heart disease and revealed aspirin resistance in 27.4% of the analyzed subjects. The causes of weak response to ASA include: obesity [5], reduced absorption [6], drug interactions [7], hyperglycemia, hypercholesterolemia, oxidative stress [8], or increased catecholamine concentrations [9]. The etiology of resistance to acetylsalicylic acid is multifactorial. Weber *et al.* put forward a pharmacological classification of abnormal response to ASA, distinguishing its three subtypes: pharmacokinetic resistance, pharmacodynamic resistance, and pseudo-resistance to aspirin. The researchers demonstrated that one of the most common reasons for the apparent lack of ASA's efficacy is patient non-compliance: skipping doses or lack of aspirin use [10]. According to some reports, approx. 40% of cardiovascular patients use ASA irregularly [11, 12]. Numerous studies list factors that increase blood platelet activity and can be responsible for reduced response to ASA, including: diabetes, obesity, nicotinism, arterial hypertension, hypercholesterolemia, heart failure, acute coronary syndrome, as well as postoperative status after coronary angioplasty or coronary artery bypass grafting [13]. The use of acetylsalicylic acid in secondary prophylaxis reduces the risk of serious cardiovascular events. Recommending ASA in the primary prophylaxis of cardiovascular disease (CVD) always requires one to estimate the trade-off between the benefits of its antiaggregatory properties and the risk of bleeding; the issue continues to be a matter of debate among experts. There is a tendency not to recommend ASA for primary prophylaxis, which stems from meta-analysis results indicating that ASA use is associated with increasing the risk of serious bleeding [14]. According to the current guidelines of the Polish Society of Hypertension, acetylsalicylic acid dosed at 75 mg can be administered to patients with arterial hypertension and high (20–30%) or very high (> 30%) global cardio-vascular risk (assessed with the Framingham Risk Score). In turn, ASA administration is not recommended when the risk is low or intermediate. Therapy should be started after the normalization of arterial pressure values in order to minimize possible adverse effects. According to the European Society of Cardiology (ESC) guidelines on CVD prevention in clinical practice from 2016, ASA should not be used in patients who are not diagnosed with CVD due to the increased risk of serious bleeding. The Antithrombotic Trialists' Collaboration published data from 6 studies encompassing 95,000 subjects; the authors investigated the role of prevention in individuals without cardiovascular or cerebrovascular disease, comparing patients receiving ASA with a control group. The results indicated a 12% reduction in the risk of serious cardiovascular events (0.51% aspirin group vs. 0.57% control group; $p = 0.0001$) and a 20% reduction in infarction risk per year. The incidence of serious (fatal or requiring blood transfusion) gastrointestinal and extracranial hemorrhages increased by 0.03% per year. The risk of vascular mortality was unaffected by the use of ASA [15]. The year 2011 saw the publication of a meta-analysis of 9 randomized prospective clinical studies encompassing over 100,000 patients without atherosclerotic symptoms. The publication evaluated the influence of acetylsalicylic acid vs. placebo on the occurrence of fatal and non-fatal cardiovascular events as well as serious hemorrhages. In the ASA group, the cardiovascular incident risk increased by 10%, while the risk of major bleeding rose by 62% in comparison to the control group. For every 1,000 patients treated with ASA over the period of 5 years, aspirin prevented 3 cardiovascular events and caused 3 major hemorrhages. The results were deemed insufficient to recommend the use of ASA for primary CVD prevention in patients without clinical evidence for atherosclerosis [16]. The American College of Chest Physicians recommends the use of ASA prophylaxis (75–100 mg) in individuals over 50 years of age with high stratified risk of CVD occurrence, even if they have no symptomatic cardiovascular disease [17]. The American Diabetes Association (ADA), American College of Cardiology (ACC), and American Heart Association (AHA) recommend the use of ASA for primary prophylaxis in diabetics with > 10% risk of cardiovascular episodes, but without an increased risk of gastrointestinal bleeding. This patient group includes: women > 60 years and men > 50 years with 1 or more risk factors (dyslipidemia, arterial hypertension, nicotinism, microalbuminuria, or family history of premature CVD) [18].

Standardized tomato extract in the primary prophylaxis of ischemic heart disease

The importance of diet (low in animal fats, rich in fruits and vegetables) is underscored in the prophylaxis of cardiovascular disease. According to the report by the World Health Organization (WHO) from 2002, low consumption of fruits and vegetables is responsible for 31% of cases of ischemic heart disease and 11% of strokes around the world [19].

Tomatoes are a particularly valuable dietary component; their properties are well-established, and they play an significant role in preventing cardiovascular disease. They are an important source of vitamins, mineral components, an biologically active compounds with antiaggregatory and anti-inflammatory properties, reducing arterial pressure and offering health benefits. Tomatoes are rich in potassium, an element indispensable for regulating cardiac rhythm and controlling arterial pressure, as well as the antioxidant vitamins C and E [20]. Standardized tomato extract (STE) is a water-soluble tomato concentrate without lycopene or fats, containing 37 biologically active compounds of established structure. These compounds include nucleosides (adenosine, cytidine, guanosine, inosine, AMP, GMP), poly-

phenols (including flavonoids: rutin, quercetin, kaempferol, luteolin, naringenin), and phenolic acids (chlorogenic, caffeic, p-coumaric, ferulic) [21, 22]. Standardized tomato extract is approved for trade in two forms: syrup and powder. In 2009, the European Food Safety Authority (EFSA) approved water-soluble tomato concentrate (WSTC) as a dietary agent helpful in maintaining proper aggregation of blood platelets. EFSA recommends the use of STE in healthy individuals between the ages of 35 and 70. The effective daily dose was established at 3 g of bioactive compounds in syrup or 65–150 mg in powder [23, 24]. The document was based on the results of 8 human and 7 animal studies [23]. Dutta-Roy *et al.* published a study 2001, which investigated antiplatelet properties of various fruits and vegetables *in vitro*. Among all the studied substances, tomato products exhibited the highest antiaggregatory activity, followed by grapefruit, melon, and strawberry products. Tomato extract inhibited ADP- and collagen-induced aggregation by as much as 70% without inhibiting blood platelet aggregation induced by arachidonic acid and the accompanying synthesis of thromboxane. O'Kennedy *et al.* studied healthy individuals, demonstrating that factors contained in water-soluble tomato extract exhibited antiplatelet activity both *in vitro* and *in vivo*. In a randomized double-blinded crossover study conducted among 90 healthy individuals aged 45–70, the authors evaluated the impact of tomato extract on platelet aggregation. The amount of bioactive substances contained in the extracts that were added to beverages received by the patients was equivalent to that contained in 2–6 fresh tomatoes. Tomato extract equivalent to 6 tomatoes caused a 17.5% reduction in collagen-induced platelet aggregation as well as a 7.8% and 21.3% reduction in ADP-induced aggregation (at 7.5 and 3 μmol ADP/l, respectively). The effect of aggregation inhibition was observed in 97% of participants. Another study, conducted among 47 healthy individuals, demonstrated similar effects of a single dose of STE and 75 mg of acetylsalicylic acid in terms of antiplatelet action (PFA-100 closure time) and influence on thromboxane A2 synthesis. When ASA was administered over 7 days, the PFA-100 closure time was three times longer than in the case of a single aspirin dose, which indicates that the effect of platelet aggregation inhibition exerted by acetylsalicylic acid is three times stronger than that of STE in chronic therapy.

Standardized tomato extract inhibits platelet aggregation in response to ADP, collagen, arachidonic acid, and thrombin *in vitro* [24]. The mechanism of STE action is multidirectional. Among other things, studies demonstrated that polyphenols influence the inhibition of fibrin aggregation, secretion, and binding by blocking protein disulfide isomerase (PDI). Tomato extract blocks receptors for ADP, collagen, and von Willebrand factor; it prevents the activation of the αIIbβ3 integrin, inhibits the activation of the GPIIb/IIIa glycoprotein, and inhibits the expression of P-selectin on the platelet surface. Standardized tomato extract also increases the concentration of cAMP and cGMP in platelet cytosol. Standardized tomato extract components are likely responsible for inactivating tissue factor (TF), a protein activating the extrinsic pathway of the coagulation cascade [25, 26]. *In vitro* animal and human studies demonstrated that tomato extract inhibits the activation of inflammatory processes in the endothelium, countering the development of atherosclerosis. Standardized tomato extract was shown to reduce the production of inflammatory cytokines (TNF-α, IL-1β, IL-12) and increase the synthesis of the anti-inflammatory interleukin 10 [27]. Moreover, phenolic acids contained in tomato extract were shown to inhibit the expression of the nuclear factor κB (NF-κB) transcription factor, which participates in inflammatory response in the course of atherosclerosis [28]. It has also been demonstrated that STE reduces the expression of cell adhesion molecules (ICAM-1, VCAM-1) in endothelial cells, which play an important role in the formation of atherosclerotic plaque [27]. Furthermore, there are reports describing the role of hypotensive properties of STE polyphenols in the mechanism of angiotensin-converting enzyme (ACE) inhibition [29]. In 2015, the guidelines of the Polish Society of Hypertension for the first time allowed the use of other substances (including STE) as alternatives to ASA. In view of these recommendations, the use of antiaggregatory preparations whose effects were confirmed by clinical studies (e.g., STE) can be considered for primary prophylaxis in patients with uncomplicated arterial hypertension and moderate or high cardiovascular risk [15].

It is noteworthy that, while STE action is reversible, ASA action is not. In this context, the former preparation appears to be a safer option for primary antiaggregatory prevention.

In conclusion, arterial hypertension constitutes an important risk factor for cardiovascular diseases, which are the most common cause of death worldwide. In patients with conditions from this group, primary prophylaxis is aimed at combating and modifying cardiovascular risk factors by promoting healthier lifestyles and introducing preventive pharmacotherapy. Statins and acetylsalicylic acid have been proven effective in this regard. The latter can relatively often lead to serious bleeding, including central nervous system or gastrointestinal bleeding. Therefore, ASA is recommended for all patients after CVD episodes (as secondary prophylaxis), but its use for primary prophylaxis continues to be debated. The risk of adverse effects associated with the use of acetylsalicylic acid warrants the search for alternative, safer substances with antiplatelet action, but with no adverse effects. Standardized tomato extract with its reversible (and thus safer) antiplatelet action may be one such substance. The results presented above demonstrate the efficacy of STE in inhibiting platelet aggregation in hypertensive patients. This may suggest that arterial hypertension patients without previous CVD episodes can benefit from the use of STE in primary prophylaxis.

Disclosure

Authors report no conflict of interest.

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