

Favourable hypotensive effect after standardised tomato extract treatment in hypertensive subjects at high cardiovascular risk: a randomised controlled trial

Beata Krasieńska¹, Angelika Osińska¹, Aleksandra Krasieńska², Maciej Osiński³, Piotr Rzymiski⁴, Andrzej Tykarski¹, Zbigniew Krasieński⁵

¹Department of Hypertension, Angiology, and Internal Disease, Poznan University of Medical Sciences, Poznan, Poland

²Medical Faculty, Poznan University of Medical Sciences, Poznan, Poland

³Department of Obstetrics, Gynaecology, and Gynaecological Oncology, Division of Reproduction, Poznan University of Medical Sciences, Poznan, Poland

⁴Department of Environmental Medicine, Faculty of Health Sciences, Poznan University of Medical Sciences, Poznan, Poland

⁵Department of General and Vascular Surgery, Poznan University of Medical Sciences, Poznan, Poland

Abstract

Background: Cardiovascular (CV) diseases remain a leading global cause of death. Lowering blood pressure (BP) reduces the risk of CV complications, especially stroke and acute coronary events, and it delays the progression of kidney disease. Adequate non-pharmacological treatment improves the effectiveness of the antihypertensive therapy. A Mediterranean diet with high content of vegetables (rich in tomatoes) is associated with a reduced CV risk.

Aim: The main objective of the present study was to assess whether the addition of standardised tomato extract (STE) or acetylsalicylic acid (ASA) to standard antihypertensive therapy can improve BP control in patients with arterial hypertension (HT).

Methods: The study involved 82 high-risk hypertensive patients. Patients with primary HT at high to a very high total CV risk were randomised in a blinded fashion to one of two groups, i.e. the ASA and STE group. The patients had two visits, a baseline visit and one after four weeks of treatment. In all the patients, during each visit, clinical BP and ambulatory BP measurements (ABPM) were performed. Platelet aggregation was determined using the VerifyNow analyser.

Results: After four weeks of treatment in the STE group, there was a statistically significant reduction in 24-h systolic BP, diastolic BP, and mean arterial pressure values measured in ABPM ($p < 0.001$). After four weeks of treatment in the STE group there was a statistically significant reduction in pulse pressure (PP) during the daytime and during 24 h ($p < 0.05$). Interestingly, it was found that the use of STE in obese patients significantly decreased the day PP ($p < 0.05$). After four weeks of treatment in the ASA group there was no statistically significant reduction in BP values measured in ABPM.

Conclusions: The results of this study show that the addition of STE to standard antihypertensive therapy improves BP control in hypertensive patients with high CV risk. This effect, together with the anti-aggregatory effect, may indicate the pleiotropic effect of tomato extract. This fact justifies further research into functional foods and gives new insights into STE as a food supplement that could have new therapeutic and prophylactic uses for the treatment of hypertensive patients with high CV risk and especially with obesity.

Key words: extract of tomato, aspirin, hypertension, cardiovascular risk

Kardiol Pol 2018; 76, 2: 388–395

Address for correspondence:

Beata Krasieńska, MD, PhD, Department of Hypertension, Angiology, and Internal Disease, Poznan University of Medical Sciences, ul. Długa 1/2, 60–848 Poznań, Poland, e-mail: bkrasinska@poczta.onet.pl

Received: 18.09.2017

Accepted: 19.10.2017

Available as AoP: 08.11.2017

Kardiologia Polska Copyright © Polskie Towarzystwo Kardiologiczne 2018

INTRODUCTION

Hypertension (HT) is one of the most common health problems in developed countries. Lowering blood pressure (BP) reduces the risk of cardiovascular (CV) complications, especially stroke and acute coronary events, and it delays the progression of kidney disease. The strategy for HT treatment should include pharmacological therapy and modification of CV risk factors [1, 2]. Adequate non-pharmacological treatment improves the effectiveness of antihypertensive therapy. Therefore, it is important to reduce weight, limit sodium intake to 75–100 mmol/d, and use the proper diet. In recent years increased interest in the use of natural food ingredients as functional foods in HT treatment has been observed. A diet rich in fruit and vegetables is associated with a reduced CV risk [1–3]. The available data support the view of the beneficial effect of the Mediterranean diet with a high content of vegetables (rich in tomatoes) and fruit due to its activity, which results in CV risk reduction [4]. Tomatoes (*Lycopersicon esculentum* L.) are the most popular and extensively consumed vegetables in the world. They are a source of bioactive compounds of anti-oxidative action such as L-ascorbic acid, polyphenols, isoflavonoids, and carotenoids (lycopene, beta-carotene) [5–8]. The consumption of tomatoes can potentially reduce or delay the development of CV disease by anti-aggregation, antihypertensive, antidiabetic, antioxidative, antiangiogenic, and protective endothelial effects [5, 7]. In a previous study, the authors investigated the anti-aggregation effect of the standardised tomato extract (STE) in hypertensive patients with high CV risk. As shown in the previous study, daily use of STE can influence the anti-platelet effect, which is heterogeneous and may be weight-dependent [9]. The mechanism of hypotensive effect of the extract is not fully explained. It is assumed, however, that it can reduce expression of renin and angiotensin-converting enzyme (ACE) [10]. Another mechanism through which STE can potentially lower BP is via an increase of the nitric oxide production, which subsequently leads to vasodilation [11]. There are also reports that the addition of low-dose acetylsalicylic acid (ASA) to antihypertensive medications can reduce both systolic (SBP) and diastolic BP (DBP) by improved endothelial function [12].

The main objective of the present study was to assess whether the addition STE or ASA to standard antihypertensive therapy can improve BP control in patients with HT.

METHODS

Study design

The study involved 82 high-risk hypertensive patients (44 men and 38 women), aged 28–74 years. It was conducted between July 2015 and February 2017 in the Department of Hypertension at the University of Medical Sciences in Poznan. Seventeen patients withdrew their consents during the study. The study was approved by the Local Bioethical Committee of Poznan University of Medical Sciences (permission no.

377/15) and was therefore performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All patients undersigned written consent forms. The study was listed in the Registration and Results System and obtained the following ClinicalTrials.gov ID: NCT03206944. Patients with primary HT and high and very high total CV risk were randomised in a blinded fashion (a sealed envelope principle) to one of two groups [13]: group 1 ASA included 33 patients who received additionally standard hypotensive therapy ASA at a dose of 75 mg in the morning; group 2 STE included 32 patients receiving STE (ZAAX, Sequoia, Poland) at a dose of 213 mg orally in the morning. The patients had two visits: at baseline and after four weeks of treatment, based on the scheme presented in Figure 1. There were no changes in the concomitant treatment (lipid-lowering, antihypertensive, and antidiabetic), and no non-steroidal anti-inflammatory drugs were taken during the study. There were no differences in the amount and type of antihypertensive drugs between the groups.

Exclusion criteria for the study were as follows: secondary HT, white coat HT, coronary artery disease, myocardial infarction, revascularisation, stroke, transient ischaemic attack, peripheral arterial disease, congestive heart failure, chronic kidney disease (glomerular filtration rate < 30 mL/min), addiction to alcohol and psychotropic substances, active cancer, congenital or acquired haemostatic disorder, and use of ASA, STE, or other antiplatelet agents within 14 days prior to the study. Additional exclusion criteria for group 2 were hypersensitivity to ASA and active gastric or duodenal ulcers.

Blood pressure measurements

In all the patients, during each visit, clinical BP measurements were performed three times at rest, in a supine position, in standard conditions, and using an upper-arm BP monitor (Omron 7051T). Ambulatory, 24-h BP measurements (ABPM) were carried out using an A&D 24-h ambulatory peripheral BP monitor. The frequency of measurements was every 15 min between 7:00 and 22:00, and every 30 min between 22:00 and 7:00. Subsequently, mean arterial pressure (MAP) was calculated from the formula $MAP = DBP + 1/3(SBP - DBP)$ (mmHg), and pulse pressure (PP) was calculated from the formula $PP = SBP - DBP$ (mmHg).

VerifyNow® test procedure

Whole blood samples were collected at 1–4 h from a peripheral vein using a 21-gauge needle in a partial fill 3.2% citrate vacuum collection tube, after the ingestion of a morning dose of ASA or STE.

The VerifyNow System is a point-of-care, turbidimetry-based optical detection system that measures platelet-induced aggregation (Accumetrics Inc., USA). In the study, two types of VerifyNow test kits were used: VerifyNow Aspirin Test and VerifyNow P2Y12. Platelet function was measured at

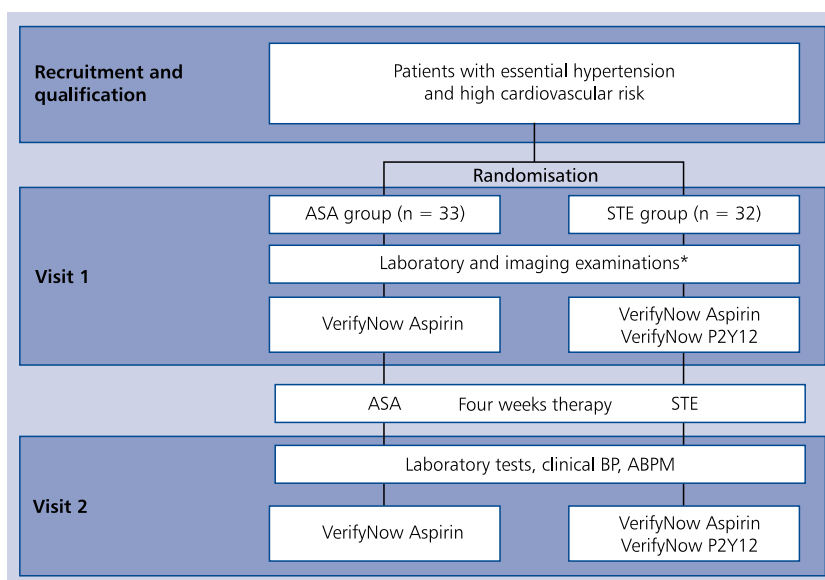


Figure 1. Scheme of the study. *In each group: laboratory tests, abdominal ultrasound examination, abdominal computed tomography scan, Doppler ultrasound of renal arteries, clinical blood pressure (BP) (3 ×/24 h), ambulatory BP measurements (ABPM), electrocardiogram, echocardiography, weight and body mass index assessment

baseline and after four weeks of treatment. In the ASA group, the VerifyNow Aspirin test was assayed. Due to the possibility of pleiotropic action of STE, in group 2, the VerifyNow Aspirin and P2Y12 VerifyNow tests were performed.

VerifyNow Aspirin assay contains lyophilised fibrinogen-coated beads and a platelet agonist — arachidonic acid. It is designed to measure platelet function based on the ability of activated platelets to bind fibrinogen. Fibrinogen-coated microparticles aggregate in whole blood in proportion to the number of unblocked platelet glycoprotein IIb/IIIa receptors. Light transmittance increases as activated platelets bind and aggregate fibrinogen-coated beads. The instrument measures this change in the optical signal caused by aggregation. Assay results are reported as aspirin reaction units (ARU), which are calculated as a function of the rate of aggregation. ARU values < 550 indicate an effective inhibition of platelet aggregation by ASA, while ARU values > 550 indicate no effect of the drug. The VerifyNow P2Y12 test in this assessment measures adenosine phosphate-induced platelet aggregation as an increase in light transmittance and utilises an appropriate algorithm to report values in P2Y12 reaction units (PRUs) and the percentage of inhibition. A higher PRU count reflects greater P2Y12-mediated platelet reactivity and points to the lack of expected antiplatelet effect.

Statistical analysis

Statistical analyses were performed with Statistica, version 12.5 (StatSoft, USA). Because the tested data did not meet the assumption of Gaussian distribution (evaluated with Shapiro-Wilk method) non-parametric methods were applied.

The Wilcoxon signed-rank test was used for evaluation of the differences between the initial values and the values obtained after the treatment, for factors of body weight composition, BP, and platelet aggregation. To evaluate the differences and correlations between the two independent groups the Mann-Whitney U test and Spearman's rank correlation coefficient (R_s) were used, respectively. The data presented in the graphs and tables include median and interquartile ranges. A p -value < 0.05 was considered significant.

RESULTS

The detailed demographic data of the studied groups are presented in Table 1. There were no statistically significant differences ($p > 0.05$) between these groups for age and body mass index (BMI) (Table 1). The baseline blood and lipid profile parameters in both groups did not show statistically significant differences ($p > 0.05$), except for the higher triglyceride concentration in the STE group (Table 2; $p < 0.05$). No changes in these parameters in any of the groups were observed after four weeks of therapy ($p < 0.05$ in all cases). At baseline, the BP values measured in ABPM were significantly ($p < 0.05$) higher in the STE group than in the ASA group (Table 3). There were statistically significant positive correlations between day SBP and the PRU values ($R_s = 0.5$, $p < 0.05$) and between 24-h SBP and PRU values ($R_s = 0.45$, $p < 0.01$) in the STE group after four weeks of treatment (Table 4). After four weeks of treatment in the STE group there was a statistically significant reduction in 24-h SBP, DBP, and MAP values measured in ABPM ($p < 0.001$; Fig. 2). After four weeks of treatment in the STE group there was

Table 1. Characteristics of patients treated with acetylsalicylic acid (ASA) or standardised tomato extract (STE) at visit 1 (median and interquartile range)

	ASA group (n = 33)	STE group (n = 32)
Female/male	19/14	8/24
Age [years]	53 (44–63)	54.5 (45.0)
BMI [kg/m ²]	31.1 (27.4–36.3)	27.7 (25.3–33.4)
BMI group:		
Normal (18.5–24.9 kg/m ²)	5	6
Overweigh (25.0–29.9 kg/m ²)	9	11
Obesity (≥ 30.0 kg/m ²)	18	14
Smokers	4	4
Concomitant lipid-lowering therapy	29	28
Concomitant antidiabetic therapy (metformin)	2	2
Concomitant therapy (anti-hypertensive)	2.9	3.2
Diuretics/aldosterone antagonists	25/8	22/6
ACEI	24	23
Angiotensin II receptor antagonists	15	13
Calcium antagonists	11	10
Beta-blockers	17	16
Alpha-blockers	1	2
ARU	574 (541–628)	582 (533–604)
PRU	Not done	228 (149–309)

ACEI — angiotensin-converting enzyme inhibitors; ARU — aspirin reaction units; BMI — body mass index; PRU — P2Y12 reaction units

a statistically significant reduction in values of pulse pressure during the daytime and 24 h ($p < 0.05$; Fig. 3). Interestingly, it was found that the use of STE in obese patients significantly ($p < 0.05$) decreased the day PP ($p < 0.05$; Fig. 4). Side effects, such as bleeding, were not recorded in either of the groups. In the present analysis, ASA resistance was confirmed in 24.2% of patients (eight of 33 patients), all characterised by BMI > 30 kg/m².

DISCUSSION

The role of ASA in primary prevention of CV diseases has been consistently reduced, mainly because of the risk of serious bleeding [5, 9]. The aim of the current study was to examine whether STE could be an alternative safe and anti-aggregatory agent that could be used instead of ASA in individuals with high CV risk. During the study, it was observed that both ASA and STE added to standard therapy affect BP as well as

Table 2. Blood parameters (median and interquartile range) for the acetylsalicylic acid (ASA) group and standardised extract of tomato (STE) group at baseline

Parameter	ASA group	STE group
GLC [mmol/L]	5.6 (5.1–6.3)	5.8 (5.2–6.2)
TG [mmol/L]*	1.0 (0.8–1.4)	1.6 (1.1–2.2)
LDL [mmol/L]	2.8 (2.3–3.4)	2.5 (2.1–3.3)
TC [mmol/L]	4.9 (4.3–5.2)	5.1 (4.0–5.6)
HDL [mmol/L]	1.3 (1.1–1.7)	1.2 (1.0–1.5)
Na [mmol/L]	141 (139–143)	142 (140–143)
K [mmol/L]	4.3 (4.1–4.6)	4.2 (3.9–4.6)
Creatinine [μ mol/L]	79.0 (70.9–87.9)	92.1 (69.9–111.5)
Urid acid [μ mol/L]	271.0 (196.0–312.0)	313.0 (251.0–348.6)
Haemoglobin [mmol/L]	9.0 (8.7–9.4)	9.3 (8.8–10.0)
Haematocrit [%]	40 (40)	40 (40–50)
Platelets [10 ⁹ /L]	241.0 (189.0–276.0)	223.0 (204.0–257.5)

*Statistically significant difference between ASA group and STE group ($p < 0.05$, Mann-Whitney U test); GLC — glucose; HDL-C — high-density lipoprotein cholesterol; LDL-C — low-density lipoprotein cholesterol; TC — total cholesterol; TG — triglyceride

antiplatelet action. Despite the widespread use of ASA, in the literature there are few reports of ASA hypotensive effects [14]. Therefore, it was decided to publish data on the effect of the two agents, i.e. STE and ASA on BP.

After four weeks of treatment with STE at 213 mg/day and ASA at 75 mg/day a significant reduction in SBP, DBP, and MAP in ABPM was achieved only in the STE group. The study group included hypertensive patients with high and very high CV risk according to the 2013 European Society of Cardiology/European Society of Hypertension (ESC/ESH) classification [13]. The study groups did not differ in terms of the dose and type of antihypertensive drugs as well as statins and antidiabetic drugs. More importantly, during the study there were no changes in the antihypertensive, lipid-lowering, and antidiabetic therapy. Similar results were reported by Engelhardt et al. [15], who achieved reduction in SBP and DBP after two months of STE at a dose of 250 mg/day, compared to a placebo group. In this study, only patients with newly diagnosed HT at the first stage without concomitant diseases were examined. However, in contrast to the current study, antihypertensive and lipid lowering therapy was not used [15].

Due to the initial objective of the study (assessment of the anti-aggregatory properties) the patients were not assigned to the groups according to BP values. Therefore, the ASA and STE study groups had significantly different BP values at baseline. The STE group on the first visit had higher BP values in daytime and 24-h analysis. However, it is this antiplatelet agent added to standard therapy that proved to lower BP significantly. Several possible mechanisms of hypotensive action of STE

Table 3. Results of ambulatory blood pressure (BP) monitoring for the acetylsalicylic acid (ASA) group and standardised extract of tomato (STE) group at visit 1

	ASA group	STE group
	Median (interquartile range); min–max	
BP day [mmHg]		
SBPd*	130.0 (123.0–139.0); 112–176	141.5 (125.5–149.0); 113–185
DBPd*	77.0 (72.0–84.0); 65–109	84.5 (76.0–92.5); 68–118
MAPd*	94.5 (89.0–103.0); 81–131	103.0 (93.0–112.0); 85–139
HRd	72.0 (66.0–80.0); 54–94	74.0 (69.0–80.0); 49–92
BP night [mmHg]		
SBPn	113.0 (108.0–123.0); 95–154	120.0 (109.5–126.5); 101–167
DBPn	66.0 (63.0–72.0); 49–93	69.0 (64.0–78.0); 56–87
MAPn	80.0 (78.0–90.0); 64–111	85.0 (80.0–95.0); 72–110
HRn	61.0 (57.0–67.0); 50–87	62.0 (54.0–66.0); 45–73
24 BP [mmHg]		
SBP24*	125.0 (120.0–137.0); 109–170	137.5 (122.0–143.0); 111–181
DBP24*	74.0 (70.0–81.0); 63–106	80.5 (74.0–88.0); 65–111
MAP24*	91.0 (87.0–99.0); 78–127	99.0 (91.0–107.0); 84–131
HR24	70.0 (64.0–77.0); 53–93	71.0 (66.0–76.0); 48–88

*Statistically significant difference between ASA group and STE group ($p < 0.05$, Mann-Whitney U test); BP — blood pressure; SBPd — ambulatory daytime systolic blood pressure; DBPd — ambulatory daytime diastolic blood pressure; MAPd — ambulatory daytime mean blood pressure; HRd — heart rate in the day; SBPn — ambulatory night time systolic blood pressure; DBPn — ambulatory night time diastolic blood pressure; MAPn — ambulatory night time mean blood pressure; HRn — heart rate in the night; SBP24 — 24-h systolic blood pressure; DBP24 — 24-h diastolic blood pressure; MAP24 — 24-h mean blood pressure HR24 — heart rate in 24 h

have been described in the literature, including beneficial effects on the endothelium [16]. This is especially important in the pathophysiology of primary HT. In its progression there is a reduction in the release of nitric oxide, increasing in the secretion of endothelin-1 and other vasoconstrictors and causing the impairment of vascular compliance [17]. Other cardio-protective features of STE are relevant. STE contains biologically active compounds that, apart from anti-atherosclerotic properties, have a multi-action effect on platelet aggregation by inhibiting platelet aggregation in response to

Table 4. Correlation (Spearman's rank correlation coefficient) between percentage change in blood pressure parameters and PRU and ARU values in standardised extract of tomato group

Percentage of change in blood pressure parameters after four weeks of treatment	Percentage of change in receptor activity after four weeks of treatment	
	PRU	ARU
SBPd	0.50**	0.32
DBPd	0.16	0.19
MAPd	0.23	0.32
HRd	–0.29	0.07
SBPn	–0.04	0.01
DBPn	–0.04	–0.05
MAPn	–0.09	0.07
HRn	0.32	–0.03
SBP24	0.45*	0.28
DBP24	0.14	0.18
MAP24	0.20	0.28
HR24	–0.14	0.09

* $p < 0.05$; ** $p < 0.01$; ARU — aspirin reaction units; PRU — P2Y₁₂ reaction units; SBPd — ambulatory daytime systolic blood pressure; DBPd — ambulatory daytime diastolic blood pressure; MAPd — ambulatory daytime mean blood pressure; HRd — daytime heart rate; SBPn — ambulatory night time systolic blood pressure; DBPn — ambulatory night time diastolic blood pressure; MAPn — ambulatory night time mean blood pressure; HRn — heart rate at night; SBP24 — 24-h systolic blood pressure; DBP24 — 24-h diastolic blood pressure; MAP24 — 24-h mean blood pressure; HR24 — 24-h heart rate

adenosine di-phosphate (ADP), collagen, arachidonic acid, and thrombin [7, 15, 16, 18–20]. Armoza et al. [21] also confirmed antihypertensive properties of STE, suggesting also a mechanism dependent on improved endothelial function. Increased nitric oxide release and reduced endothelin-1 were demonstrated with the addition of this extract [21]. Other suggested mechanisms of antihypertensive action of STE are calcium channel blocking, direct vasodilatation, decreasing chymase activity, and inhibition of ACE and renin expression [8]. The main sources of ACE inhibitors in food are peptides, flavonoids, and polyphenols. It has been shown that plant extracts rich in flavonoids are natural, and competitive to synthetic ACE inhibitors displaying the BP lowering properties [10]. This mechanism of ACE inhibition is a recognised, effective method for treating patients with HT and high CV risk [13]. The current work has also shown the beneficial effect of STE on PP. High values of this parameter (over 60 mmHg) are independent CV risk factors in hypertensive patients (ESC/ESH 2013) [16, 22, 23]. Progressive vascular stiffness resulting from the vasoconstriction-vasodilatation disorder observed in HT is the primary mechanism responsible for increasing the difference between SBP and DBP, i.e. the rise in PP.

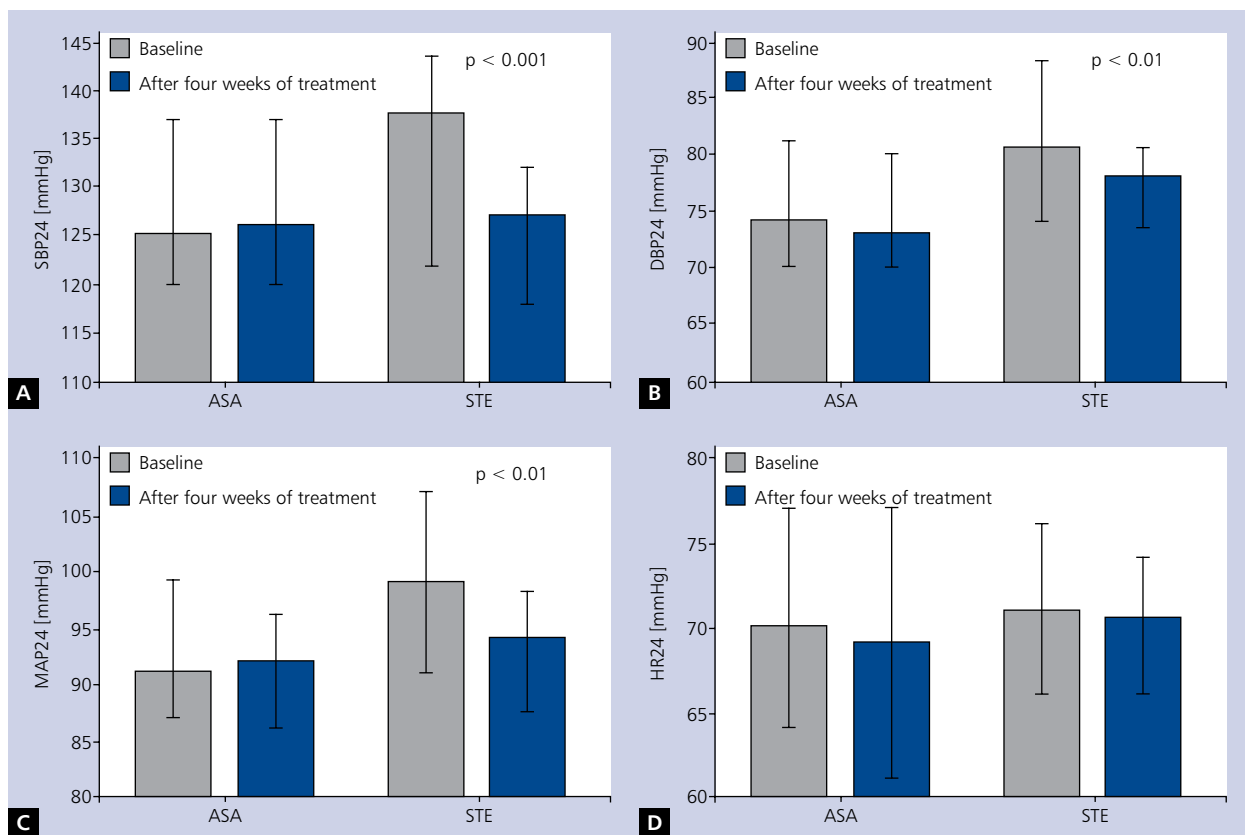


Figure 2. A–D. The results of ambulatory BP measurements (ABPM) for acetylsalicylic acid (ASA) group and standardised extract of tomato (STE) group at baseline — visit 1 (grey bars) and after four weeks of treatment (blue bars) — visit 2. Reported p-value for Wilcoxon signed-rank test; SBP24 — 24-h systolic blood pressure; DBP24 — 24-h diastolic blood pressure; MAP24 — 24-h mean blood pressure; HR24 — heart rate in 24 h

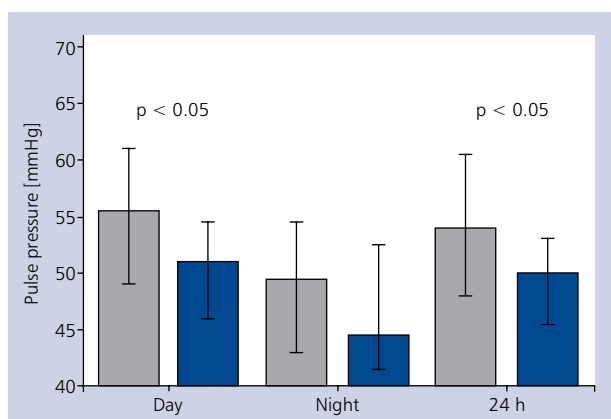


Figure 3. The pulse pressure during the daytime, night time, and 24 h, for the standardised tomato extract group at baseline — visit 1 (grey bars) and after four weeks of treatment (blue bars) — visit 2. Reported p-value for Wilcoxon signed-rank test

In the present study, after four weeks of treatment with STE a significant decrease in PP during daytime (8.8%) and in the 24-h analysis (8.1%) (Fig. 3) was observed. There was

also a statistically significant decrease in PP during the day in the obese patients taking STE, and this could indicate improved elasticity of large arteries (Fig. 4). This is an important observation for this group of patients in which the superiority of STE over ASA was demonstrated in terms of antiplatelet effects [9].

The PP values determine the stiffness in the arterial system and may be important in the development of complications in the progression of HT. It has been shown that in the elderly, CV risk is directly proportional to PP, and it has a strong predictive value of the 10-year risk of CV mortality [24]. In the current study, in the ASA group, there was no significant decrease in BP after four weeks of treatment. The results are consistent with those published by Avanzini et al. [25], where after three months of treatment with 100 mg ASA daily there was no difference in SBP and DBP between the treatment and control groups. Different results have been published by Magen et al. [12], who demonstrated that adding a low dose of ASA in hypertensive patients improves endothelial function and reduces BP compared to a control group. A similar hypotensive effect of ASA, dose and time of administration dependent, has been observed in patients with mild HT [24].

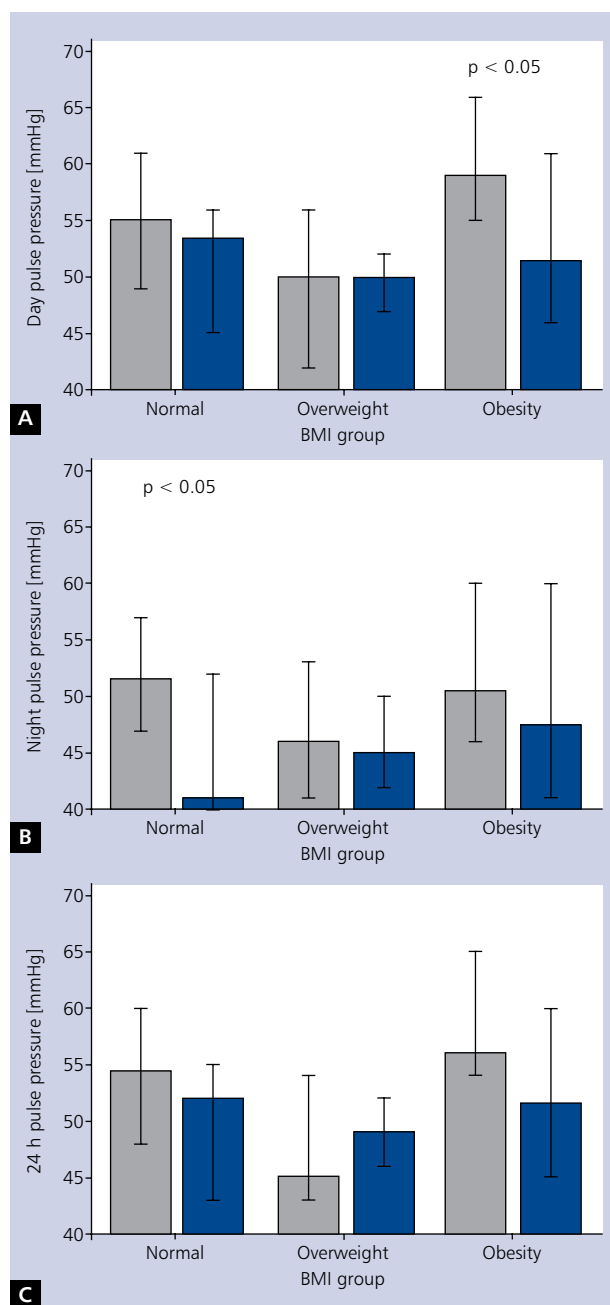


Figure 4. The pulse pressure at day (A), night (B), and 24 h (C) reported as median and interquartile range for patients ($n = 32$) treated with standardised tomato extract at baseline (grey bars) and after four weeks of treatment (blue bars) depending on body mass index (BMI). The reported p -value is for Wilcoxon signed-rank test

In the present study, there was also a significant positive correlation between SBP in the daytime and in the 24-h period and the percentage change of P2Y12 receptor activity measured in PRU. This parameter indicates increased platelet aggregation induced by ADP, which plays a key role in the development of arterial thrombosis. The decrease in PRU

values demonstrates a reduction in P2Y12 receptor activity and has beneficial antiplatelet effects (Table 4). In a previously published paper, a beneficial anti-aggregatory effect of STE was reported in obese hypertensive patients [9]. The present results and previous conclusions may indicate pleiotropic effects of STE.

Limitations of the study

Although the present study provides new information on the clinically beneficial properties of STE, some study limitations should be stressed for a cautious interpretation of the results. Firstly, the duration of therapy in our study was relatively short, and it did not answer the question of whether this beneficial antihypertensive effect of STE would be maintained over a longer follow-up. Also, the study groups were relatively small, although it should be pointed out that previous studies regarding the impact of STE on CV risk were also carried out in groups of similar size. This highlights the need for further long-term follow-up studies in larger groups. It should also be noted that there was a significant difference in the baseline BP parameter values between the ASA and STE groups. This was caused by the recruitment of patients according to antiplatelet properties, so that the ARU values did not differ at the baseline visit.

CONCLUSIONS

The results of this study show that the addition of STE to standard antihypertensive therapy improves BP control. This short-term treatment with antioxidant-rich tomato extract can reduce both the BP and PP in hypertensive patients with high CV risk. Additionally, the present study proved that there is a positive correlation between BP and the P2Y12 receptor activity, which may indicate the pleiotropic effect of tomato extract. This fact justifies further research into functional foods and gives new insights into STE as a food supplement that could have new therapeutic and prophylactic uses for the treatment of hypertensive patients with high CV risk and especially with obesity.

Conflict of interest: none declared

References

1. Podolec P, Filipiak KJ, Undas A, et al. Polish Forum for Prevention Guidelines on Prophylactic Pharmacotherapy: update 2017. *Kardiol Pol.* 2017; 75(5): 508–511, doi: [10.5603/KP.2017.0087](https://doi.org/10.5603/KP.2017.0087), indexed in Pubmed: [28530029](https://pubmed.ncbi.nlm.nih.gov/28530029/).
2. Tykarski A, Narkiewicz K, Gacjong Z, et al. 2015 guidelines for the management of hypertension. Recommendations of the Polish Society of Hypertension - short version. *Kardiol Pol.* 2015; 73(8): 676–700, doi: [10.5603/KP.2015.0157](https://doi.org/10.5603/KP.2015.0157), indexed in Pubmed: [26304155](https://pubmed.ncbi.nlm.nih.gov/26304155/).
3. Kłosiewicz-Latoszek L, Szostak WB, Podolec P, et al. Polish forum for prevention guidelines on diet. *Kardiol Pol.* 2008; 66(7): 812–814, indexed in Pubmed: [18690577](https://pubmed.ncbi.nlm.nih.gov/18690577/).
4. Obarzanek E, Sacks FM, Vollmer WM, et al. DASH Research Group. Effects on blood lipids of a blood pressure-lowering diet:

- the Dietary Approaches to Stop Hypertension (DASH) Trial. *Am J Clin Nutr.* 2001; 74(1): 80–89, indexed in Pubmed: [11451721](#).
5. Osińska A, Osiński M, Krasieńska A, et al. Antiplatelet treatment in the primary prophylaxis of cardiovascular disease in patients with arterial hypertension. *Kardiochir Torakochirurgia Pol.* 2017; 14(2): 133–136, doi: [10.5114/kitp.2017.68745](#), indexed in Pubmed: [28747946](#).
 6. Burton-Freeman B, Talbot J, Park E, et al. Protective activity of processed tomato products on postprandial oxidation and inflammation: a clinical trial in healthy weight men and women. *Mol Nutr Food Res.* 2012; 56(4): 622–631, doi: [10.1002/mnfr.201100649](#), indexed in Pubmed: [22331646](#).
 7. Miazga A, Kostka-Jeziorny K, Begier-Krasieńska B, et al. Standardized tomato extract — is an alternative to aspirin in the primary prevention of cardiovascular disease in patients with hypertension. *Arter Hypertens.* 2014; 18: 37–42.
 8. Huang WY, Davidge ST, Wu J. Bioactive natural constituents from food sources-potential use in hypertension prevention and treatment. *Crit Rev Food Sci Nutr.* 2013; 53(6): 615–630, doi: [10.1080/10408398.2010.550071](#), indexed in Pubmed: [23627503](#).
 9. Krasinska B, Osińska A, Osinski M, et al. Standardised tomato extract as an alternative to acetylsalicylic acid in patients with primary hypertension and high cardiovascular risk – a randomised, controlled trial. *Arch Med Sci.* 2017, doi: [10.5114/aoms.2017.69864](#).
 10. Biswas D, Uddin MdM, Dizdarevic LL, et al. Inhibition of angiotensin-converting enzyme by aqueous extract of tomato. *Eur J Nutr.* 2014; 53(8): 1699–1706, doi: [10.1007/s00394-014-0676-1](#), indexed in Pubmed: [24573416](#).
 11. Woźakowska-Kapłon B, Filipiak K, Mamcarz A, et al. The standardized tomato concentrate therapy in primary cardiovascular disease prevention. Is it an alternative to aspirin and for whom? An expert consensus document. *Folia Cardiol.* 2015; 10(2): 100–105.
 12. Magen E, Viskoper JR, Mishal J, et al. Effects of low-dose aspirin on blood pressure and endothelial function of treated hypertensive hypercholesterolaemic subjects. *J Hum Hypertens.* 2005; 19(9): 667–673, doi: [10.1038/sj.jhh.1001910](#), indexed in Pubmed: [16034448](#).
 13. Mancia G, Fagard R, Narkiewicz K, et al. Task Force Members. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens.* 2013; 31(7): 1281–1357, doi: [10.1097/01.jjh.0000431740.32696.cc](#), indexed in Pubmed: [23817082](#).
 14. Costa AC, Reina-Couto M, Albino-Teixeira A, et al. Aspirin and blood pressure: Effects when used alone or in combination with antihypertensive drugs. *Rev Port Cardiol.* 2017; 36(7-8): 551–567, doi: [10.1016/j.repc.2017.05.008](#), indexed in Pubmed: [28684123](#).
 15. Engelhard YN, Gazer B, Paran E. Natural antioxidants from tomato extract reduce blood pressure in patients with grade-1 hypertension: a double-blind, placebo-controlled pilot study. *Am Heart J.* 2006; 151(1): 100, doi: [10.1016/j.ahj.2005.05.008](#), indexed in Pubmed: [16368299](#).
 16. Schwager J, Richard N, Mussler B, et al. Tomato Aqueous Extract Modulates the Inflammatory Profile of Immune Cells and Endothelial Cells. *Molecules.* 2016; 21(2): 168, doi: [10.3390/molecules21020168](#), indexed in Pubmed: [26840280](#).
 17. Safar ME. A reappraisal of clinical research on arterial stiffness in hypertension in France. *J Am Soc Hypertens.* 2016; 10(6): 482–488, doi: [10.1016/j.jash.2016.04.004](#), indexed in Pubmed: [27189796](#).
 18. O’Kennedy N, Raederstorff D, Duttaroy AK. Fruitflow®: the first European Food Safety Authority-approved natural cardio-protective functional ingredient. *Eur J Nutr.* 2017; 56(2): 461–482, doi: [10.1007/s00394-016-1265-2](#), indexed in Pubmed: [27388464](#).
 19. European Food Safety Authority (EFSA). Water-soluble tomato concentrate (WSTC I and II) and platelet aggregation. *EFSA J.* 2009; 7(5): 1101, doi: [10.2903/j.efsa.2009.1101](#).
 20. Ried K, Frank OR, Stocks NP. Dark chocolate or tomato extract for prehypertension: a randomised controlled trial. *BMC Complement Altern Med.* 2009; 9: 22, doi: [10.1186/1472-6882-9-22](#), indexed in Pubmed: [19583878](#).
 21. Armoza A, Haim Y, Bashiri A, et al. Tomato extract and the carotenoids lycopene and lutein improve endothelial function and attenuate inflammatory NF-κB signaling in endothelial cells. *J Hypertens.* 2013; 31(3): 521–9; discussion 529, doi: [10.1097/HJH.0b013e32835c1d01](#), indexed in Pubmed: [23235359](#).
 22. Blacher J, Staessen JA, Girerd X, et al. Pulse pressure not mean pressure determines cardiovascular risk in older hypertensive patients. *Arch Intern Med.* 2000; 160(8): 1085–1089, doi: [10.1001/archinte.160.8.1085](#), indexed in Pubmed: [10789600](#).
 23. London GM, Cohn JN. Prognostic application of arterial stiffness: task forces. *Am J Hypertens.* 2002; 15(8): 754–758, doi: [10.1016/s0895-7061\(02\)02966-7](#), indexed in Pubmed: [12160201](#).
 24. Hermida RC, Fernández JR, Ayala DE, et al. Influence of aspirin usage on blood pressure: dose and administration-time dependencies. *Chronobiol Int.* 1997; 14(6): 619–637, doi: [10.3109/07420529709001452](#), indexed in Pubmed: [9360028](#).
 25. Avanzini F, Palumbo G, Alli C, et al. Effects of low-dose aspirin on clinic and ambulatory blood pressure in treated hypertensive patients. Collaborative Group of the Primary Prevention Project (PPP)–Hypertension study. *Am J Hypertens.* 2000; 13(6 Pt 1): 611–616, doi: [10.1016/s0895-7061\(00\)00231-4](#), indexed in Pubmed: [10912743](#).

Cite this article as: Krasieńska B, Osińska A, Krasieńska A, et al. Favourable hypotensive effect after standardised tomato extract treatment in hypertensive subjects at high cardiovascular risk: a randomised controlled trial. *Kardiol Pol.* 2018; 76(2): 388–395, doi: [10.5603/KPa2017.0215](#).