Archives of Clinical Hypertension

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Research Article

Usefullness of Phytoestrogens in Treatment of Arterial Hypertension. Systematic Review and Meta-Analysis: Un Update

Abstract

Background: It has been suggested that phytoestrogens may have utility in the control of arterial hypertension.

Methods: We performed a systematic review and meta-analysis of randomized controlled trials, and the main outcome was the decrease of blood pressure.

Results: Decrease in systolic (- 0,15 mmHg, CI 95% from -0,24 to -0,05) and diastolic (-0,14 mmHg, CI 95% from -0,25 to -0,03) blood pressure were observed in patients taking phytoestrogens, but this difference was not clinically relevant. There can be a little greater decrease in Asian patients and in patients with higher baseline blood pressure values.

Conclusion: The global effect of phytoestrogens seems of small amount in reducing blood pressure. Nevertheless, it has not been realized a clinical trials about the efficacy of these products in no mild hypertensive patients, similar to real life.

Introduction and Background

Soy is a legume of Asian origin that contains 2 main components, phytoestrogens (PHE) and soy protein (SP), whose beneficial effects on the cardiovascular system (among other) have been studied over the last 30 years. It has been described its benefits to improve lipid and glycemic profiles, as well as to reduce the harmful effects of cardiovascular (CV) risk factors. Other benefits attributed to soy and its derivate (PHE and SP) are: reduce the symptoms associated with menopause, osteoporosis fractures and progression of metastatic cancers (prostate, breast, lung, stomach, etc).

It has been suggested that PHE may have utility in the control of arterial hypertension. This disease affects 1000 millions of people all around the world and is a modifiable cardiovascular risk factor [1]. Its prevalence in adults is elevated (26,4%) [2], with an improbable control [3]. An increase of BP (20/10 mmHg) is associated with doubling the risk of CV disease, and on the other side, reductions of 4-5/2-3 mmHg are associated with lower risk of CV disease [4,5]. Adecuate dietary intervention with proper medical therapy are important in controlling blood pressure (BP) according to American Heart Association (AHA) and the Seventh Report of the Joint National Committee (JNC 7) [4,6].

The Food and Drug Administration (FDA) has recommended intake of 25 g of SP [7], to leverage its cardio protective effects, which could be related to its agonist action on estrogenic receptor. The main described PHE are isoflavones (IF) and their active principles daidzein and genistein. They could produce arterial vasodilatation, improvement of endothelial function and decrease of BP in animals, all these effects mediated by nitric oxide mechanisms [8]. Previous clinical trials and meta-analysis [9-11], have previously shown inconsistent results: results without statistical significance or with little clinical impact [9], statistically significant reduction of systolic BP (SBP) [10], or statistically significant reduction of SBP and diastolic BP (DBP) [11]; these differences could be due to the different trials included in the numerical analysis, and different aspects of it (length of intervention, parallel vs cross-over design, amount of used active principle –IF or SP-, etc).

To clarify the usefulness of PHE in reducing BP, we performed a new systematic review and meta-analysis. It has been considered this time aspects such as: age of participants, the fact that BP is –or isn´t- the primary outcome in the design of the study, country, etc. In addition, several metaregresions have been performed to assess the mathematical relationship between BP reduction achieved and the initial BP, the dose of active principles, etc.

Material and Methods

Our systematic review is aimed at randomized clinical trials involving adult patients (older than 18 years), hypertensive and non-hypertensive, and the main objective of the study were controlling BP, cholesterol and other lipids levels, symptoms associated with menopause, osteoporosis, diabetes mellitus (including chronic complications), metastatic breast and lung cancer, etc.

The intervention in these studies was the addition of PHE, in capsule form or dietary supplement. The estimated IF (mg) or SP (g) daily amount was noted. The control treatment was placebo or an inactive derivate (milk protein, casseinate, etc). The measured result

was the decrease in systolic and diastolic blood pressure during the study period.

This systematic review was registered on the web PROSPERO.

We have also made searching several databases such as PubMed, Embase, ClinicalTrials.gov, Trip Database and CENTRAL data base of Cochrane collaboration. The search strategy PUBMED was: "Phytoestrogens" (Mesh) OR "Isoflavones"(Mesh) OR "Soy Foods"(Mesh) OR "Soybeans"(Mesh) OR "daidzein" (Supplementary concept); filters: Clinical Trial Phase III; Clinical Trial Phase IV; Systematic Reviews; Humans. We obtained 197 studies (clinical trials and meta-analysis). The other search strategies were similar (Table A, Appendix).

We also looked for systematic reviews and meta-analysis reviews obtained through searches in PUBMED and Trip Database, although the primary outcome may or may not be the control of BP. We have not included in this search works published only in Chinese or Japanese language.

The analysis of the original works and data collection was carried out by pairs (MAG and MAR); in case of differences of opinion, the point of view of a third researcher (LPL) was required. The manuscript was translated into English by another researcher (AMC). The final review of the work was done by the four authors.

We have made an estimation of decrease in systolic and diastolic BP between the end of the active period and the initial moment. In all studies assessed, it has been measured BP at the start and at the end of intervention, in each treatment arm. The variables retrieved from the original work has been the variation of BP and standard deviation (SD). In those works where these data are described, they are incorporated directly into the estimation; in those works that didn´t include these data, calculations are made as described in Appendix. We performed a meta-analysis with a weighted mean difference according to the random effects model (Der Simonian and Laird) assessing the possible statistical heterogeneity between estimated effect in the included studies.

Study quality was estimated by Jadad´s scale [12], and with the risk of bias tool of the Cochrane collaboration. Finally, we have considered the Impact Factor of the journal where the work was published.

We valued the presence of publication bias using the funnel plot, and calculating the number of unpublished studies (Glesser-Olkin method). The presence of statistical heterogeneity was assessed using the Cochran - Q index and I 2 index. Finally we assessed the effect of small studies in the overall estimate with the Egger´s graphical method.

Statistical calculators and graphics were performed by STATA v.14 and REVMAN v.5.3 (Cochrane collaboration).

Results

Flow-chart of evaluated and excluded studies are shown in Figure 1. After removing duplicate works and leaving out systematic reviews and observational studies, we finally left 346 clinical trials. Most of them (246) were not included because no BP was measured in them. Finally our work includes 100 clinical trials, and 71 were included in the mathematical elaboration (meta-analysis).

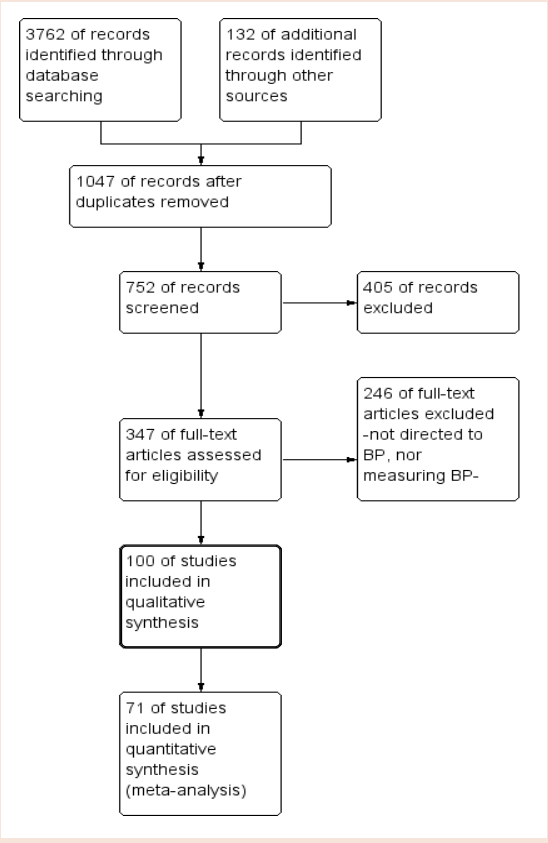

Figure 1: Flow-chart describing included studies on our work.SS.

The characteristics of included studies are shown in Table B (Appendix). The average age of included patients is between 50-65 years; patients are probably non-hypertensive (some works are planned in pre-hypertensive and grade 1 hypertensive patients, hypertensive patients are excluded in other works, and information about inclusion of hypertensive patients is absent in other jobs); and there are a greater percentage of included women in these works (with a high proportion of postmenopausal and non-taking hormone replacement therapy women). Active treatments are PHE administered in capsules, sachets or simply dietary recommendations. Control treatments were either placebo or probably inactive principles (milk protein, casein). The duration of intervention was variable, from 4 weeks to 2 years. The primary outcome of a lot of studies was not the reduction of BP, but variations in lipid profile or menopausal symptoms.

The methodological quality of included studies, or their risk of bias, is summarized en Figure 2. Most of them are described as double blind and randomized, although the description of blinding or randomizing methods is usually insufficient. 55 works (75%) have been conducted in western countries (22 USA, 11 Australia, 9 Italia,

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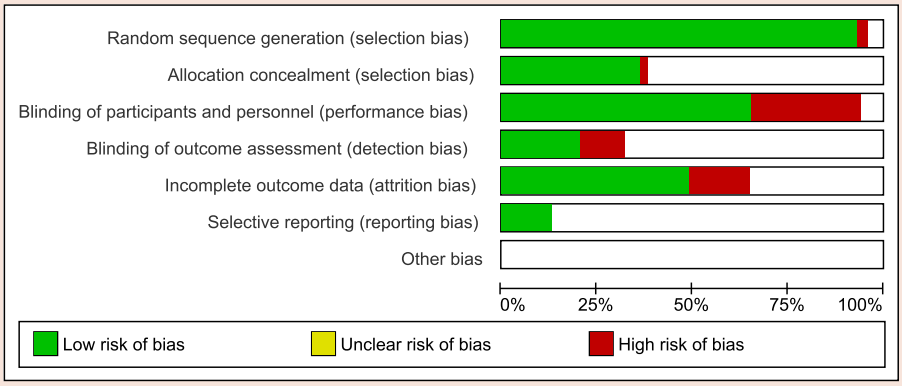

Figure 2: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

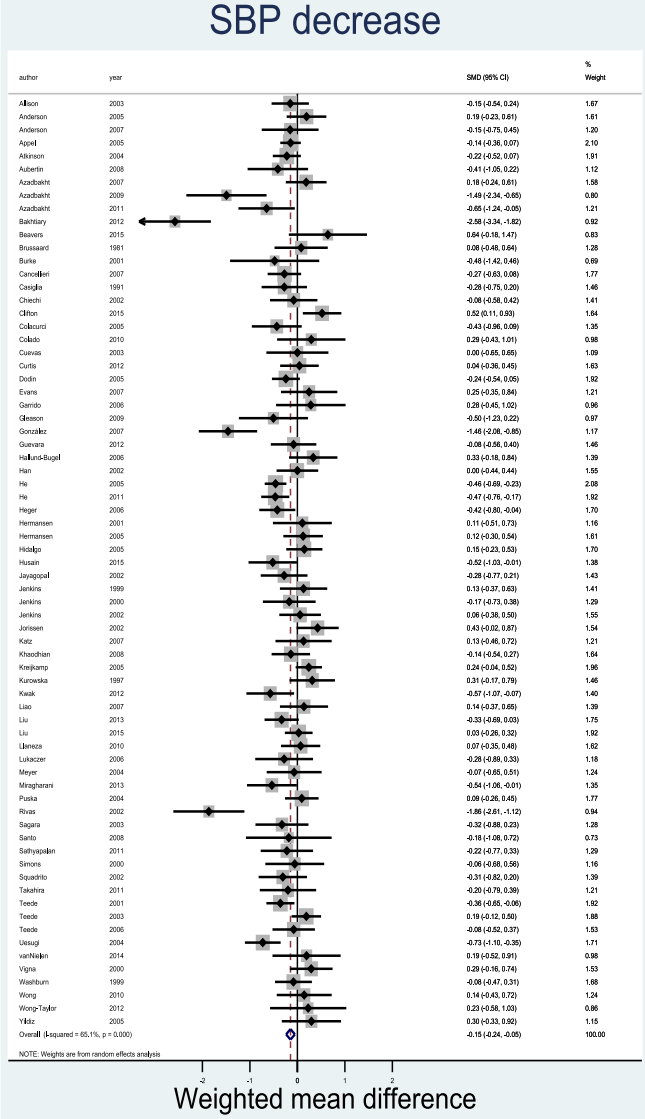

Figure 3: Forest plot of systolic blood pressure decrease of all studies included in the meta-analysis.

etc), and the remaining 16 in Asian countries (7 Iran, 5 China, 2 Japan, etc).

There is no numeric data of decrease of BP in 25 studies (references included in Appendix #7, 17, 18, 20, 29, 34, 35, 37, 45, 46, 47, 48, 49, 51, 62, 63, 69, 73, 74, 75, 76, 78, 84, 91 and 93); most of them show results that are not statistically significant. In others, even though the measurement of BP is mentioned in their Method section, this is not included in the Results section; and one study (# 99) divided the data in 2 groups, equal producers and non-producers, a situation that does not allow an appropriate mathematical operation. Other 4 studies (references #25, 72, 86 and 97) expressed results with trend to greater reduction of BP with PHE, but with impossible mathematical management. We finally have processable numerical results from 71 studies, and with these meta-analysis was performed.

Figure 3 shows the global evaluation of the achieved reduction in systolic BP (SBP) comparing active treatment with the control arm. The found difference is statistically significant (-0,15 mmHg SBP drop, CI 95% from -0,24 to -0,05) but lacks clinical impact. The high value of Q (p< 0,00001) and I^2 (65%) agree with the presence of a high degree of statistical heterogeneity. Sensitivity analyses including studies that were primarily aimed (Figure 4) at control of BP shows similar results. Finally, the isolated analysis of works that provides BP SSdifference and SD (Figure A, Appendix) shows, as in the previous cases, results of limited clinical relevance. We found similar results in the evaluation of reduction in diastolic BP (DBP) in the global evaluation (Figure B), in the sensitivity analysis of primary directed to BP control studies (Figure C) and in the evaluation of studies which show difference of DBP and SD (Figure D, Appendix). Findings with DBP decrease are similar to those described with SBP; we have presented results in relation with SBP decrease.

The graphical representation of possible publication bias is shown in Figure 5. It can be seen in the funnel plot that a majority distribution of studies are around the mean estimation; the point of 4 papers are relatively far from the central point cloud, with estimations that show greater reductions in systolic BP (between -2,6 and -1,5 mmHg); on the other hand, no works were seen with similar estimations on the other side of the point cloud. Instead, calculating unpublished studies by the method of Glesser Olkin (Table C, Appendix) shows a negative result (i.e., probably there is no non-identified study to discover).

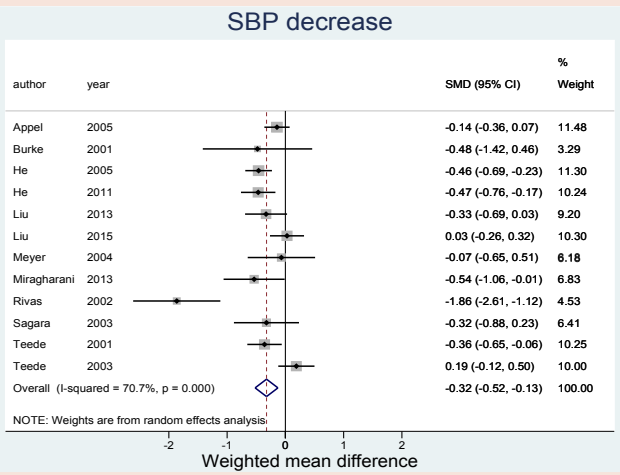

Figure 4: Forest plot of systolic blood pressure decrease of studies whose primary outcome was decrease of blood pressure.

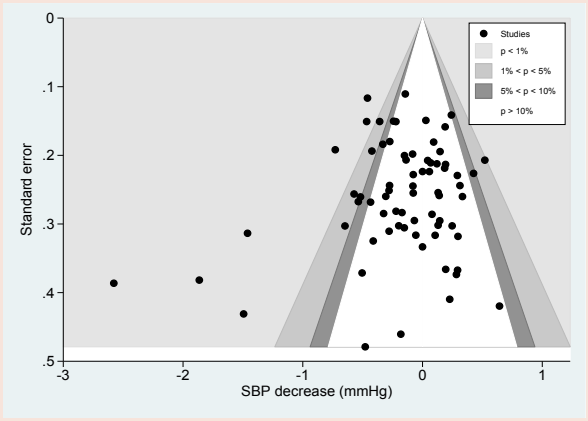

Figure 5: Funnel plot of included studies in the meta-analysis.

Figure E (Appendix) shows a weighted line of effects in large and small studies, suggesting that there is not an effect of small studies.

The BP lowering observed in works of greater and lesser quality are similar, with similar effects regardless of the quality of study (evaluated by Jadad´s scale [12], comparing 2 subgroups (>= 3 points –better quality- vs < 3 points –bad quality-)(Figure F, Appendix) and with meta-regression (Figure G, Appendix). There is also no difference in comparison of parallel vs cross-over studies (Figure H, Appendix).

A slight difference in effect is seen in Asian countries (SBP -0,40 mmHg, CI 95% -0,66 to -0,14) compared with western countries (SBP -0,08 mmHg, CI 95% -0,17 to 0,01) (Figure 6). This difference is statistically significant but seems not clinically relevant.

Metaregression assessment by the amount of active principle administered shows inconclusive results (Figures I and J, Appendix). The slope of the regression line is substantially horizontal in both groups, suggesting that the limited achieved effect is independent of the amount of administered IF / SP. There is also no relationship between BP lowering achieved with the length of treatment (Figure K, Appendix).

The observed SBP decline is slightly higher in patients with higher initial systolic BP values (Figure 7), although this decrease is again neither statistically significant nor clinically relevant (additional decrease of 0,5 mmHg comparing basal BP of 150-160 mmHg vs 100-110 mmHg). There is also no decrease in SBP according to the proportion of included women in the study, the mean age of included population, or Impact Factor of the journal where the work was published (Figures L, M and N, Appendix). Additional data are included in Table E (Appendix).

Discusion

The results of our work are simple, and point in the same direction of our previous work [8]. Treatment with PHE achieved a not clinically important lowering of systolic and diastolic BP, even with higher amount of active principle and longer period of treatment. This is the same result found with studies were the primary outcome was BP. No difference was found even if we consider patient´s age and gender, type of study (parallel or cross-over) or methodological quality.

We can consider PHE /soy derivatives as pharmaconutrients, i.e., elements with nutritional characteristics and beneficial pharmacological properties. With this pharmacological aspect, it seems therefore important the administered dose and length of treatment. It would be logical that with a greater amount or duration of treatment, greater reduction in BP is achieved. However, this Figure is not observed in our study, because (perhaps) there is a little overall reduction in BP. Other works describe that commercial preparations often contain a mixture of ingredients of unknown concentrations [13,14], there can be genetic differences, as equal producers seem to present a more positive response to PHE intervention in treating perimenopausal symptoms [15] and probably in treating hypertension; differences have been reported in the prevalence of equol producer phenotype among different ethnicities, with higher prevalence in soy consuming Asian than in western populations [16], it is probably related to years of adaptation of Asians to soy, and by supposed beneficial effects of soy, should not be extrapolated to whites and other ethnicities who historically had no contact with soy [13]. By last, soy consumption per capita, according to United Nations Organization (ONU) data, is < 1 g/day in most European or North American countries, except vegetarians or Asian immigrants [17], it is found that soy consumption in Asian countries is 20-50 g/day [18] and increased consumption of PHE is associated with higher circulating levels of phytoestrogens and their metabolites. Several observational studies developed in Japan, with higher intake of PHE, show less cardiovascular and tumoral disorders [19,20], but the answer to this question may be in the lifestyle, and not only in the intake of these products.

Certainly, our work has limitations. Included patients have little co-morbidity, and frequently are no defined as hypertensive or non-hypertensive. Despite the huge efforts made to find most clinical trials, it is very difficult to exclude the existence of works focused on

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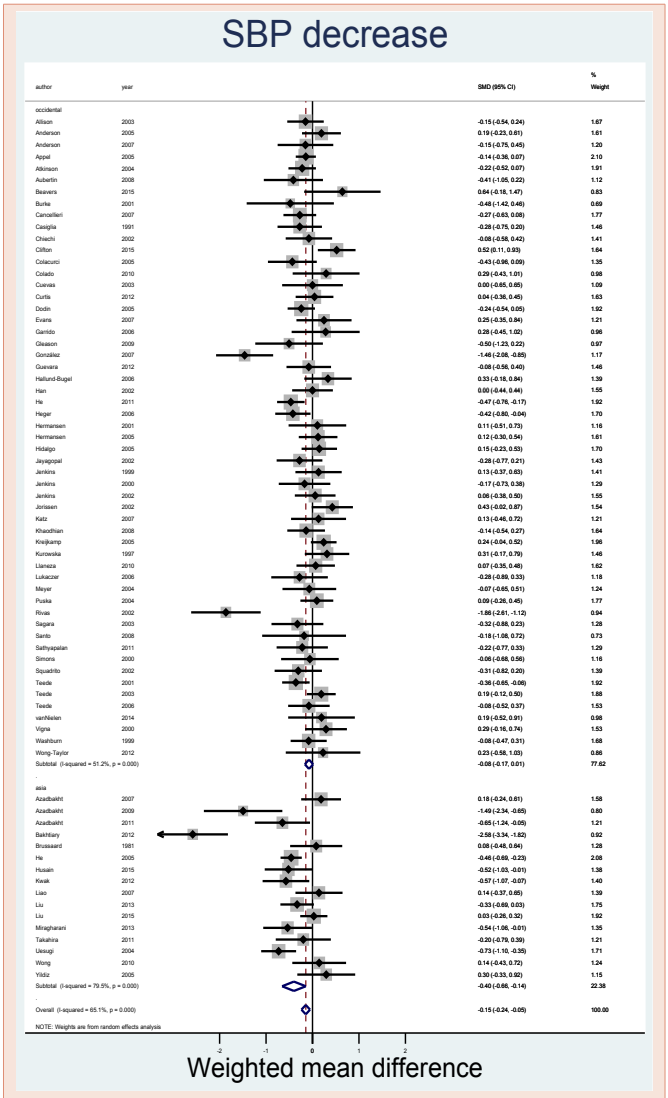

Figure 6: Sensitivity analysis of studies developed in western vs Asian countries.

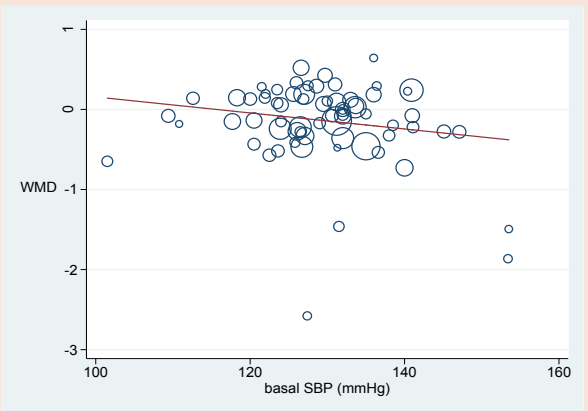

Figure 7: Scatter plot and regression line to evaluate relationship between systolic blood pressure decrease and initial systolic blood pressure.

hypertensive patients or with significant co-morbidities. The absence of numeric results in 29 studies (mostly with commentaries as "not significant differences"), and the potencial presence of reporting bias (BP measured but not registered) make it less likely that taking PHE is associated with decrease in BP. The decision of not including (by language difficulty) original Chinese or Japanese works can take away the option of a more positive effect (in these countries there seems to be a higher effect). The net effect of these opposite limitations seems to be neutral. Also, mathematical calculation of standard deviation (SD) could not be totally correct; given the absence of data in original studies, it was decided to make this approach; nevertheless, the estimated mean difference seems correct (not biased), and maybe it is just an erroneous approach of the dispersion (SD) of that value; either way, the sensitivity analysis including only works that shows these values (difference in BP and SD) gives similar results.

In a literature review [21], the ability of PHE to reduce BP is showed -in this work authors do not show any trial without BP declining, as we show in our work-. However, with a less comprehensive obtaining of studies, they suggest the concept that soy supplement may be beneficial during the development but not in established phases of hypertension [21]. Our review shows that PHE does not seem very effective in pre-hypertension or mild hypertension. In view of this reflection and our results, clinical trials with more real patients (higher degree, 2-3, of hypertension; or patients with comorbidities) must be carried out.

Conclussions

Treatment with PHE gets slight decreases of systolic and diastolic BP, with limited clinical impact. With these findings, we cannot make a recommendation of taking PHE as categorical as in the late twentieth century. It seems to be greater BP decrease in Asian populations compared with western groups, and in patients with greater baseline BP values.

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WE KNEW BEFORE

- Soy derivatives have pleiotropic and protective cardiovascular properties.
- AHA recommended their intake, based on these healthy properties.

WE KNOW NOW (WITH OUR WORK)

- Soy derivatives intake gets blood pressure decrease that is

statistically significant but not clinically important.

- Blood pressure decrease is higher in Asian populations and in patients with higher baseline levels of blood pressure.

IN THE FUTURE

- Meta-analysis can be completed including articles originally published in Chinese and Japanese.

It is important to conduct clinical trials of utility of phytoestrogens in hypertensive patients, not only prehypertensive or mild hypertensive ones.

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