Does potassium supplementation lower blood pressure? A meta-analysis of published trials

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Both epidemiologic and clinical studies have suggested that an increase in potassium intake may lower blood pressure. However, the results of prospective clinical trials looking at the effect of oral potassium supplements on blood pressure have yielded conflicting results. For this reason, we reviewed 19 clinical trials examining the same end-point and involving a total of 586 participants (412 of whom had essential hypertension). Overall, the results of the trials indicate that oral potassium supplements significantly lower systolic blood pressure [−5.9 mmHg, −6.6 to −5.2 mmHg (mean, 95% confidence interval)] and diastolic blood pressure (−3.4 mmHg, −4.0 to 2.8 mmHg). The magnitude of the blood pressure lowering effect is greater in patients with high blood pressure (−8.2 mmHg, −9.1 to −7.3 mmHg for systolic and −4.5 mmHg, −5.2 to −3.8 mmHg for diastolic blood pressure) and appears to be more pronounced the longer the duration of the supplementation ($P < 0.05$ and $P < 0.01$ for systolic and diastolic, respectively). Based on this analysis, an increase in potassium intake should be included in the recommendations for a non-pharmacological approach to the control of blood pressure in uncomplicated essential hypertension.

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Introduction

Hypertension is an important risk factor for both stroke and coronary heart disease [1] and the reduction of blood pressure levels due to treatment is associated with a significant reduction in cerebrovascular and cardiovascular morbidity and mortality [2,3].

Over the past 20 years, a large body of evidence has established a strong link between nutrition and blood pressure. For instance, the value of sodium restriction [4], weight reduction [5] and moderate alcohol consumption [6] as non-pharmacological measures for lowering blood pressure in a large proportion of patients with essential hypertension is widely recognized and general recommendations are now made [7,8].

Most recently, both epidemiologic and clinical studies have strongly suggested that an increase in potassium intake also lowers blood pressure [9,10]. However, while well designed clinical trials have clearly shown the beneficial effect of oral potassium supplement on blood pressure, other similarly well designed studies have failed to confirm this. This discrepancy has led to questions as to whether a potassium supplement does lower blood pressure and whether a moderate increase in potassium intake should be advised. There may be a number of possible explanations for the discrepancy between studies. Selection of participants, insufficient sample size, heterogeneity of blood pressure response and design of the study are among possible factors which could explain, at least in part, the conflicting results.

For this reason, we reviewed a number of clinical trials studying the effect of oral potassium supplementation on blood pressure and carried out a meta-analysis by applying a statistical procedure to all trials, thereby increasing the statistical power and allowing for differences between trials such as sample size, study design and variability in the response.

Methods

We sought out all published trials on the effect of oral potassium supplementation on blood pressure by

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reviewing reference lists in relevant papers and conducting manual (Current Contents and Index Medicus) and computer (Medline and ICI) searches of articles published between 1980 and 1989.

Our analysis was primarily designed to examine trials which featured a period of oral potassium supplementation, but randomized placebo-controlled trials were also analysed separately, as well as those carried out in hypertensive patients. When a crossover design was found, authors were approached by a standard letter and asked to provide the raw data on individual blood pressure changes in order that we could calculate the variance. For those who either did not reply or from whom data could not be obtained, an average value was attributed to the variability in both systolic and diastolic blood pressure changes, i.e. standard deviations of the differences between control and intervention. Data from studies published between 1981 and 1989 [11–28] were used. From these studies the following characteristics were recorded (Table 1).

(1) The name of the first author, year of publication, journal and country of origin.
(2) The type and design of the trial: whether it was an open, a single- or a double-blind study and whether a sequential, a parallel-group or a crossover design was used.
(3) The duration of the trial; any intermediate values reported in the studies were not considered.
(4) The number of participants, in both control (or placebo) and potassium groups, for whom complete sets of data were obtained.
(5) The mean age of the groups studied and/or the age range.
(6) The proportion of male : female and white : black participants in each study, where available.
(7) The total amount of potassium given per day and the formulation used.
(8) The average initial systolic and diastolic blood pressures recorded; where provided, readings taken when subjects were in the supine position were used; where trials include a run-in period, the blood pressure recorded at the end of the run-in period was used.
(9) The average systolic and diastolic blood pressures recorded both at the end of the control (or placebo) period and at the end of the intervention period for both supine (unless otherwise specified) and standing (where available) positions and the correspondent standard deviations.
(10) The change in the average systolic and diastolic blood pressures during intervention, i.e. the difference between blood pressure values at the end of the control (or placebo) period and those at the end of the intervention period, and the correspondent standard deviations.
(11) The average 24-h urinary sodium and potassium excretion during control (or placebo) and intervention periods, where available.
(12) The average values for plasma renin activity, plasma aldosterone and plasma (or serum) potassium during control (or placebo) and intervention periods, where available.

Some studies were not included in the analysis, either because data on blood pressure changes were not

Table 1. Characteristics of the trials included in the analysis.

Trial	Country	Type	Design	Duration (days)	No. of participants	Age (years)	Age (range)	Sex (M:F)	Race (W:B)	Dose (mmol/day)	Dose Formulation
Skrabal *et al.* [11]	Aus	O	X	14	20		(21–25)	20:0		120	mixture
Iimura *et al.* [12]	Jpn	O	X	10	20	39		11:9		100	diet
MacGregor *et al.* [13]	UK	DB	X	28	23	45	(26–66)	12:11	18:5	60	KCl
Khaw and Thom [14]	UK	DB	X	14	20		(22–35)	20:0		64	KCl
Smith *et al.* [15]	UK	O	S	12	10	56		6:4	6:4	96	KCl
Overlack *et al.* [16]	FRG	O	S	56	16	29		13:3		100	KCl
Richards *et al.* [17]	NZ	DB	X	28–42	12		(19–52)			140	KCl
Smith *et al.* [18]	UK	DB	X	28	20	53	(30–66)	11:9	18:2	64	KCl
Kaplan *et al.* [19]	USA	DB	X	42	16	49	(35–66)	6:10	3:13	60	KCl
Zoccali *et al.* [20] (a)	UK	DB	X	14	19	38	(26–53)	10:9	19:0	100	KCl (92%)
(b)	UK	O	S	5	10		(20–29)	10:0		100	KCl
Weissberg *et al.* [21]	UK	O	S	7	20	21	(19–29)	20:0		96	KCl
Matlou *et al.* [22]	UK	SB	X	42	32	51	(34–62)	0:32	0:32	65	KCl
Siani *et al.* [23]	It	DB	P	105	19 + 18	45	(21–61)	23:14	37:0	48	KCl
Svetkey *et al.* [24]	USA	DB	P	56	47 + 54	51		75:26	89:12	120	KCl
Miller *et al.* [25]	USA	O	S	28	64	42		29:35	64:0	66	K Glu and Cit
Grobbee *et al.* [26]	Neth	DB	X	42	40	24	(18–28)	34:6		72	KCl
Grimm *et al.* [27]	USA	DB	P	84	150 + 148	58		298:0		96	KCl
Obel [28]	Ken	DB	P	112	24 + 24	41	(23–56)	21:27	0:48	64	KCl

Table 1 continued.

Trial	Supine				Standing				Supine change (mmHg)		Standing change (mmHg)	
	Control		Active		Control		Active					
	SBP (mmHg)	DBP (mmHg)	SBP (mmHg)	DBP (mmHg)	SBP (mmHg)	DBP (mmHg)	SBP (mmHg)	DBP (mmHg)				
Skrabal	125.0	73.1	123.3	68.6					−1.7	−4.5		
Iimura	144.5	92.6	133.4	87.4					−11.1	−5.2		
MacGregor	155.0	99.0	148.0	95.0	155.0	105.0	147.0	105.0	−7.0	−4.0	−8.0	0
Khaw	115.7	72.1	114.6	69.6					−1.1	−2.5		
Smith	156.0	93.0	147.0	91.0	153.0	101.0	141.0	96.0	−9.0	−2.0	−12.0	−5.0
Overlack	152.0	98.0	135.0	88.0					−17.0	−10.0		
Richards	149.9	92.4	148.0	91.4	151.7	102.3	148.7	100.4	−1.9	−1.0	−3.0	−1.9
Smith	162.0	103.0	160.0	103.0	160.0	111.0	160.0	110.0	−2.0	0	0	−1.0
Kaplan	133.2	97.7	127.6	91.9					−5.6	−5.8		
Zoccali (a)	147.0	92.0	146.0	89.0	147.0	99.0	146.0	99.0	−1.0	−3.0	−1.0	0
(b)	117.0	71.0	113.0	69.0	116.0	83.0	110.0	81.0	−4.0	−2.0	−6.0	−2.0
Weissberg	123.3	61.2	118.9	61.1	120.0	84.1	119.1	83.4	−4.4	−0.1	−0.9	−0.7
Matlou	151.0	103.0	144.0	100.0					−7.0	−3.0		
Siani	145.8	92.5	131.8	82.0	145.9	98.5	134.8	91.1	−14.0	−10.5	−11.1	−7.4
Svetkey	142.0	92.4	141.1	91.1					−0.9	−1.3		
Miller	113.2	73.1	113.6	73.9					+0.4	+0.8		
Grobbee	135.7	72.5	133.2	71.9					−2.5	−0.6		
Grimm	121.8	79.5	121.6	80.1					−0.2	+0.6		
Obel	172.0	100.0	133.0	83.0	168.0	102.0	130.0	84.0	−39.0	−17.0	−38.0	−18.0

Table 1 continued.

Trial	Urinary sodium (mmol/24 h)		Urinary potassium (mmol/24 h)		Plasma potassium (mmol/l)	
	Control	Active	Control	Active	Control	Active
Skrabal	210	155	71	115	4.69	4.51
Iimura	158	183	41	123		
MacGregor	140	169	62	118	3.84	4.02
Khaw	155	164	78	130		
Smith	134	128	65	128	4.00	4.20
Overlack	181	187	66	153		
Richards	200	205	62	185	3.84	3.99
Smith	73	80	67	117	3.90	4.10
Kaplan	168	169	36	82	3.00	3.56
Zoccali (a)	182	195	58	139	3.90	4.00
(b)	112	124	59	161	3.90	4.30
Weissberg	332	341	83	178	3.80	3.90
Matlou	130	165	52	114	3.87	4.32
Siani	189	183	57	87	4.35	4.35
Svetkey					4.40	4.70
Miller	168	165	59	82		
Grobbee	57	69	74	131	3.76	4.00
Grimm	114	115	76	115	4.10	4.40
Obel	172	–	62	102	4.00	4.00

Aus, Austria; Jpn, Japan; UK, United Kingdom; FRG, Federal Republic of Germany; NZ, New Zealand; USA, United States of America; It, Italy; Neth, The Netherlands; Ken, Kenya; O, open; DB, double-blind; SB, single-blind; X, crossover; S, sequential; P, parallel group; M, male; F, female; W, white; B, black; Glu, gluconate; Cit, citrate; SBP, systolic blood pressure; DBP, diastolic blood pressure.

available [29–31], end-points other than blood pressure fall were studied [32] or potassium deprivation was compared with normal potassium intake [33].

Statistical analysis

Ninety-five per cent confidence intervals (C.I.) of the difference in blood pressure between control (or

placebo) and potassium-treated groups in each study were calculated for two samples, either paired or unpaired, according to Gardner and Altman [34] and Bulpitt [35], as shown in detail in the Appendix. The results from each study were also weighted by the inverse of the variance [36–38] and the pooled mean treatment effect and standard error and correspondent 95% C.I. were calculated as detailed in the Appendix. Weighted linear regression was used to calculate weighted slopes by weighting inversely as to the residual variances [39] (see Appendix). Ninety-five per cent C.I. of the slopes were also computed [40]. The relationship between the level of blood pressure at baseline and the blood pressure response to potassium was analysed as previously described [41].

The analysis was carried out using the University of London Computer and the Statistical Package for Social Sciences.

Results

Characteristics of trials

Table 1 contains the full details of the trials included in the present analysis. Eleven out of the 19 studies were double-blind, 10 employed a crossover design and four included a parallel-group comparison. Thirteen trials were carried out in patients with a variable degree of essential hypertension, two of which were in hypertensive patients on pharmacological treatment [19,27], and six were performed in normal subjects. A total number of 586 participants (412 of whom suffered from essential hypertension) were given oral potassium in the different trials and 240 were used in the placebo groups. Males represented approximately 76% (619 out of 814 in 18 trials) and white participants were approximately 69% (254 out of 370 in 10 trials) of the reported sex and race distribution. The mean age was 39.6 years (median 41.0 years, range 21–58 years); the average amount of potassium given (mostly as potassium chloride) was 86 mmol/day (median 96 mmol/day, range 48–140 mmol/day) and the average duration of the supplementation period was 39 days (median 28 days, range 5–112 days). The average blood pressure of the pooled sample in all trials was 140/87 mmHg (median 145/92 mmHg), with an average urinary sodium excretion of 160 mmol/24 h (median 163 mmol/24 h, range 57–332 mmol/24 h) and urinary potassium excretion of 63 mmol/24 h (median 62 mmol/24 h, range 36–83 mmol/24 h). After potassium supplement, urinary potassium excretion was 126 mmol/24 h (median 120.5 mmol/24 h, range 82–185 mmol/24 h). The average increase in urinary potassium excretion while on potassium supplementation was 63 mmol/24 h (median 56.5 mmol/24 h, range 23–123 mmol/24 h). Plasma renin activity ranged between 0.33 and 4.19 ng/ml per h (n = 7), plasma aldosterone ranged between 125 and 385 pmol/l (n = 9) and plasma potassium from 3.00 to 4.69 mmol/l (n = 15).

Effect of potassium on blood pressure

The analysis of the studies was carried out in three steps. First, we calculated the mean effect of potassium supplementation on blood pressure and the 95% C.I. of the differences for both systolic and diastolic blood pressures reported in each individual study in either the supine or the standing position. Figures 1a and 1b show the results for supine blood pressure. The effect of potassium supplement on supine blood pressure was variable, ranging from −39.0/−17.0 to +0.8/0 mmHg change. For supine systolic blood pressure, six of the 19 trials (32%) had 95% C.I. below zero (Fig. 1a), indicating a statistically significant fall in blood pressure achieved with potassium, and nine of them (47%) indicated a significant fall in diastolic blood pressure following potassium supplementation (Fig. 1b). The results for the standing blood pressure in nine of the 19 studies in which it was reported were consistent with the findings in the supine position (33% and 22%).

The second step of the analysis was to look at the results of the trials, either as a whole or considering those carried out in hypertensive patients only, or those employing a randomized placebo-controlled design. Pooled estimates of the mean effect of potassium supplementation on blood pressure, standard error and 95% C.I. were calculated by weighting the results of each individual study by the inverse of the variance (see Appendix). This procedure allows for differences in study design, sample size and for variability of responses between trials. Table 2 shows

Table 2. Pooled estimate of the treatment effect of potassium supplementation on blood pressure.

	Supine blood pressure (mmHg)	Standing blood pressure (mmHg)
All trials:	(n = 19)	(n = 9)
Systolic	−5.9 ± 0.4 (−6.6 to −5.2)	−10.1 ± 0.6 (−11.3 to −8.9)
Diastolic	−3.4 ± 0.3 (−4.0 to −2.8)	−4.7 ± 0.4 (−5.6 to −3.8)
Hypertensives only:	(n = 13)	(n = 7)
Systolic	−8.2 ± 0.5 (−9.1 to −7.3)	−11.9 ± 0.7 (−13.3 to −10.5)
Diastolic	−4.5 ± 0.4 (−5.2 to −3.8)	−5.4 ± 0.5 (−6.4 to −4.4)

Values are shown as mean ± s.e.m. (95% confidence intervals).

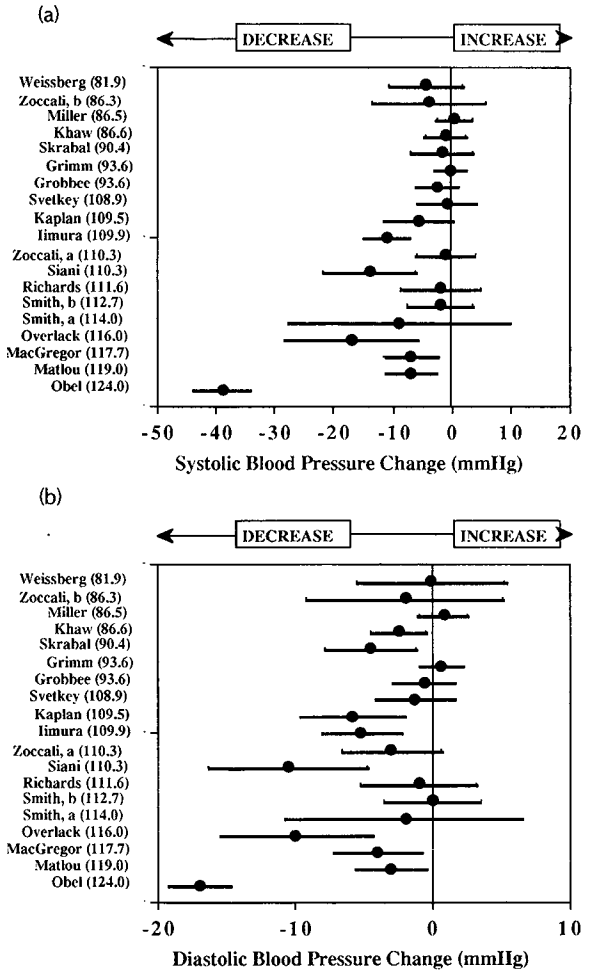

Fig. 1. Mean and 95% confidence intervals of the differences in supine (a) systolic and (b) diastolic blood pressure after oral potassium supplementation. Values in parentheses represent the average mean blood pressure during control or placebo.

these pooled estimates for both supine and standing blood pressures. When considering all trials, there was an overall significant fall in supine blood pressure of 5.9/3.4 mmHg and a significant fall in standing blood pressure of 10.1/4.7 mmHg. The size of the pooled estimate of the blood pressure lowering effect of potassium was not different when only randomized placebo-controlled trials were considered (supine blood pressure: −6.2 mmHg, pooled 95% C.I., −7.1 to −5.3 mmHg for systolic and −3.7 mmHg, −4.4 to −3.0 mmHg for diastolic; n = 12). However, the pooled estimate of the fall in both supine and standing blood pressure appeared to be greater when studies carried out in patients with essential hypertension were analysed separately (Table 2).

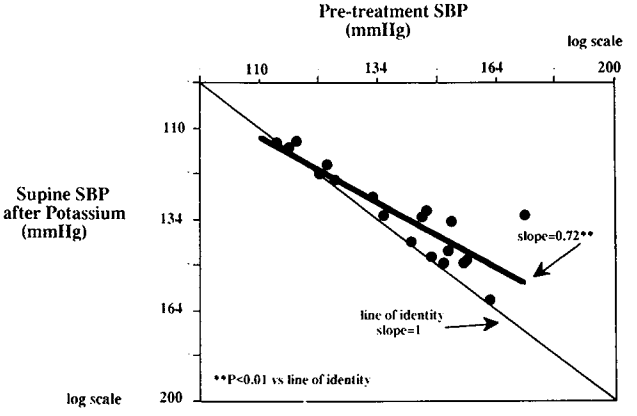

Fig. 2. Baseline (either control or placebo) supine systolic blood pressure (SBP) is plotted against the supine SBP achieved after potassium supplementation (both on a log scale). The slope of the regression line (0.72) is significantly different from the slope of the line of identity. The higher the baseline blood pressure, the greater the response to a potassium supplement.

A separate analysis was also performed after exclusion of the study by Obel [28], which appeared to represent an outlier. When considering all trials, however, there was an overall significant fall in supine blood pressure (−4.0/−2.4 mmHg, 95% C.I. −4.7 to −3.2/−3.0 to −1.8 mmHg). When the trials carried out only in hypertensive patients were analysed, the pooled estimate of the fall in supine blood pressure appeared to be greater (−5.3/−3.0 mmHg, 95% C.I. −6.2 to −4.4/−3.7 to −2.3 mmHg).

The third step was an attempt to identify possible predictors of the blood pressure response to oral potassium supplementation. The blood pressure response to potassium supplementation tended to be greater

Table 3. Pooled weighted estimate of the standardized regression coefficient (β), slope (b_w) and 95% confidence intervals (C.I.) of b_w between duration (ln) and fall in blood pressure as a dependent variable.

	Supine blood pressure (mmHg)			Standing blood pressure (mmHg)		
	β	b_w	(95% C.I. of b_w)	β	b_w	(95% C.I. of b_w)
All trials:		(n = 19)			(n = 9)	
Systolic	0.50	5.86*	(1.1 to 10.6)	0.75	9.58**	(3.3 to 15.9)
Diastolic	0.59	3.77***	(1.3 to 6.2)	0.78	5.07**	(2.1 to 8.0)
Hypertensives only:		(n = 13)			(n = 7)	
Systolic	0.49	7.29	(−0.4 to 15.0)	0.83	7.58**	(3.1 to 12.1)
Diastolic	0.59	4.77*	(0.9 to 8.6)	0.78	15.2*	(4.5 to 25.9)

*$P < 0.05$, **$P < 0.025$, ***$P < 0.01$.

the higher the initial blood pressure. The slope of the regression line (on a log/log scale) between initial and achieved supine blood pressure was 0.72 ($P < 0.01$, versus the slope of the line of identity) for systolic (Fig. 2) and 0.87 ($P \geq 0.05$, versus the slope of the line of identity) for diastolic blood pressure. This confirms the results obtained from the previous analysis, suggesting that hypertensive patients may show a greater response to an increase in potassium intake. Furthermore, the blood pressure response to potassium also appeared to be related to duration of the treatment. A weighted regression analysis (Table 3) showed that there was a significant relationship between blood pressure fall and duration of treatment (after log transformation of the latter due to the skewed distribution of values). In other words, the longer the treatment, the greater the blood pressure response to potassium. We could not perform the same analysis on other possible predictors such as hormones, level of potassium or sodium intake because raw data were not available to estimate their variance.

Discussion

The results of this overview indicate that an oral potassium supplement produced a significant reduction in supine blood pressure of 5.9/3.4 mmHg in the subjects treated overall and a greater and significant reduction in blood pressure of 8.2/4.5 mmHg in patients with high blood pressure. The effect of oral potassium on standing blood pressure was consistent and, if anything, greater.

The idea that potassium could lower blood pressure was first suggested by Addison in 1928 [42]. Since then, experimental and epidemiological observations have supported this concept [9,10]. However, when clinical investigations in humans have been undertaken, contrasting results have arisen. Clinical trials of oral potassium supplementation have clearly demonstrated a significant blood pressure lowering effect of this intervention and suggested that a moderate increase in potassium intake could be recommended in patients with high blood pressure and normal renal function. At the same time, however, similarly designed clinical trials have failed to show a significant effect of comparable amounts of potassium given as oral supplements to subjects with normal or elevated blood pressure.

Although a prospective randomized clinical trial is the best method of showing whether one treatment is better than another, sometimes large number of patients need to be recruited to detect the predicted or expected difference. Therefore, discrepancy could be expected when trials with limited patient entry may fail to refuse the null hypothesis, even though a real and useful difference exists between the results of the two treatments being compared. This is because each study may lack sufficient statistical power to detect the small difference that may reasonably be expected as a result of either the small number of subjects recruited or the difference in study design or the difference in the variability of the response to the treatment.

One method of overcoming the problem of discrepancy between the results of similar clinical trials examining the same end-point is to analyse the pooled results of those trials, a procedure named overview or meta-analysis [43–49]. The purposes are to increase statistical power for primary end-points, to resolve uncertainty when reports disagree and to improve estimates of effect size. Despite the value in demonstrating a real and useful treatment effect when single trials have failed to provide unequivocal results, the possibility of an overview should not discourage the organization of large trials and should not replace it. With this in mind, the results of our overview were able to show that a significant and useful blood pressure lowering effect could be achieved by an oral potassium supplementation. Based on the pooled estimate of both variance and effect size, it could be predicted that between 16 and 49 patients would be needed in a crossover trial to detect changes in blood pressure as those shown in the present study with a power of 90%.

The size of the effect in hypertensive patients of approximately 8/5 mmHg must also be regarded as clinically relevant. Two recent overviews of randomized trials of antihypertensive treatment have emphasized that, in prospective observational studies, a long term difference of a few mmHg in diastolic blood pressure could be associated with approximately 35–40% reduction in stroke and with a reduction in coronary heart disease estimated between 9% and 25% [2,3]. If the effect of an oral potassium supplement, such as that estimated in our overview, were maintained in the longer term, this could have many important implications. For instance, it could represent an additional non-pharmacological way of treating many patients with mild-to-moderate hypertension or could allow a reduction in the need for pharmacological antihypertensive therapy in many other patients. This would, in turn, reduce the costs for the treatment of hypertension and might also contribute to improving overall morbidity and mortality from vascular diseases. In this respect, our analysis would also suggest, although it does not prove this, that the effect of oral potassium on blood pressure may become more pronounced the longer the duration of the supplement. Furthermore, it has recently been suggested in a preliminary report, that a moderate increase in potassium intake, comparable to that achieved with oral potassium supplements in many trials, can be obtained by increasing the intake of potassium with food (fruit,

vegetables and legumes), with a significant reduction in the need for antihypertensive treatment in patients with uncomplicated essential hypertension over a period of 1 year [50]. Moreover, some epidemiological [51,52] and experimental [53] evidence suggests that high dietary potassium intake might be associated with lower incidence of stroke, also independently of the effect on blood pressure [53]. This recent suggestion renews the interest in the possible and more generalized beneficial effect of high potassium intake on vascular diseases and more studies will be needed to investigate this further.

In conclusion, the results of the present study, unlike those of a similar analysis looking at the postulated beneficial effect of oral calcium supplements on blood pressure [38], clearly show overall a small but statistically and clinically significant blood pressure lowering effect of oral potassium supplementation, suggesting that an increase in the dietary intake of potassium should be included in the general recommendations for the non-pharmacological approach to the control of uncomplicated essential hypertension.

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Appendix

The 95% confidence intervals (C.I.) of the differences in blood pressure between placebo (or control) and potassium-treated groups for each study were calculated according to Gardner and Altman [34] and Bulpitt [35].

For two unpaired samples the equation is:

$$(x_1 - x_2) - (1.96 \times SE_{diff}) \text{ to } (x_1 - x_2) + (1.96 \times SE_{diff})$$

where x_1 and x_2 are the two sample means, 1.96 is attributed to $t_{1-\alpha/2}$ taken from the t distribution with $n_1 + n_2 - 2$ degrees of freedom and SE_{diff} is the standard error of the difference between the two sample means:

$$SE_{diff} = S\sqrt{\frac{1}{n_1} + \frac{1}{n_2}}$$

where n_1 and n_2 are the sample sizes, S is the pooled estimate of the standard deviation given by:

$$S = \sqrt{\frac{(n_1 - 1)sd_1^2 + (n_2 - 1)sd_2^2}{(n_1 + n_2) - 2}}$$

For two paired samples the equation is:

$$(x_1 - x_2) - 1.96 \times s_d/\sqrt{n} \text{ to } (x_1 - x_2) + 1.96 \times s_d/\sqrt{n}$$

where s_d is the standard deviation of the difference.

In each study, the mean treatment effect is $(x_1 - x_2)$ where 1 indicates active treatment and 2 indicates control (or placebo). The pooled mean treatment effect is:

$$\frac{\Sigma\left[\frac{(x_1 - x_2)}{\sigma_d^2}\right]}{\Sigma\left(\frac{1}{\sigma_d^2}\right)}$$

and the associated standard error is:

$$\left[\Sigma\left(\frac{1}{\sigma_d^2}\right)\right]^{-\frac{1}{2}}$$

The quantity σ_d^2 is estimated as follows:

$$s_d\left(\frac{1}{n_1} + \frac{1}{n_2}\right)^{\frac{1}{2}}$$

where s_d is the standard deviation of the change in each study.

Pooled estimates of 95% C.I. were calculated as:

$$\frac{\Sigma\left[\frac{(x_1 - x_2)}{\sigma_d^2}\right]}{\Sigma\left(\frac{1}{\sigma_d^2}\right)} \pm \left[1.96\left(\Sigma\frac{1}{\sigma_d^2}\right)^{-\frac{1}{2}}\right]$$

Weighted linear regression was used to calculate a weighted slope (b_w) by weighting inversely as to the residual variances [39]:

$$\frac{\Sigma w_i x_i y_i}{\Sigma w_i x_i^2}$$

where x_i and y_i are deviations from the weighted means and w_1 is the reciprocal of the variance of ε at the given value of x. The 95% confidence intervals of the weighted slope were calculated as follows [40]:

$$b_w \pm 1.96 \times SE_{b_w}$$

where SE_{b_w} is the standard error of the weighted slope.