Effect of Antihypertensive Drug Treatment on Cardiovascular Outcomes in Women and Men

A Meta-Analysis of Individual Patient Data from Randomized, Controlled Trials

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Background: Trials of drug therapy for hypertension have shown that such therapy has a clear overall benefit in preventing cardiovascular disease. Although these trials have included slightly more women than men, it is still not clear whether treatment benefit is similar for both sexes.

Objective: To quantify the average treatment effect in both sexes and to determine whether available data show significant differences in treatment effect between women and men.

Design: Subgroup meta-analysis of individual patient data according to sex. Analysis was based on seven trials from the INDANA (INdividual Data ANalysis of Antihypertensive intervention trials) database and was adjusted for possible confounders.

Patients: 20 802 women and 19 975 men recruited between 1972 and 1990.

Interventions: Primarily β-blockers and thiazide diuretics.

Results: In women, treatment effect was statistically significant for stroke (fatal strokes and all strokes) and for major cardiovascular events. In men, it was statistically significant for all categories of events (total and specific mortality, all coronary events, all strokes, and major cardiovascular events). The odds ratios for any category of event did not differ significantly between men and women. In absolute terms, the benefit in women was seen primarily for strokes; in men, treatment prevented as many coronary events as strokes. Graphical analyses suggest that these results could be completely explained by the difference in untreated risk.

Conclusions: In terms of relative risk, treatment benefit did not differ between women and men. The absolute risk reduction attributable to treatment seemed to depend on untreated risk. These findings underline the need to predict accurately the untreated cardiovascular risk of an individual person in order to rationalize and individualize antihypertensive treatment.

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The effectiveness of antihypertensive drug treatment is well established and has been quantified in terms of overall reduction in the relative risk for stroke and other cardiovascular disease events (1, 2). Risk for cardiovascular events (especially myocardial infarction) differs greatly between men and women, and these differences are not explained by other risk factors (3). It remains unclear, however, whether the effect of antihypertensive treatment in reducing cardiovascular risk is dependent on sex.

In a 1986 review, MacMahon and colleagues (4) stated that

> event rates, particularly those for fatal events and non-fatal myocardial infarction, were substantially lower in women than in men. The striking benefits of study treatments for the risk of fatal and non-fatal stroke were evident for both men and women. A reduction in total mortality could not be demonstrated for women, but the treatment effect for women was not significantly different from that in men, among whom there was an important and statistically significant reduction in mortality.

This comment was based on the results of two trials: the Hypertension Detection and Follow-up Program (HDFP) (5) and the Medical Research Council trial of treatment of mild hypertension (MRC35-64) (6). In their 1991 analysis of data from these trials plus data from the European Working Party on High Blood Pressure in the Elderly (EWPHE) trial (7) and the Australian therapeutic trial in mild hypertension (8), Anastos and colleagues (9) concluded that

> the few data that do exist suggest that gender, like race and age, significantly influences the natural course of hypertension ... and the response to treatment .... The data regarding aggressive treatment of white women are equivocal; there is concern that such treatment may actually be harmful.

Since these reviews were published, reports of three additional trials of antihypertensive treatment in older hypertensive men and women have appeared in print: the Medical Research Council trial of treatment of hypertension in older adults (MRC 65-74) (10), the Systolic Hypertension in the Elderly Program (SHEP) (11), and the Swedish Trial in Old Patients with Hypertension (STOP) (12). More recently, other reviewers have stated that "antihyper-

tensive medications do not appear to be as effective in women as in men" (13) and that "when treated, women often achieve less benefit than do men" (14).

The INDANA (INdividual Data ANalysis of Antihypertensive intervention trials) project (15) offers the opportunity to provide more evidence on the effects of antihypertensive treatment in women; results are based on individual patient data from all of the randomized, controlled trials mentioned in the preceding paragraphs. The two main objectives of the current study are to quantify the average treatment effect in each sex separately and to determine whether treatment effect differs significantly between women and men.

Methods

The INDANA project (whose rationale, objectives, and methods are described in detail elsewhere [15]) is a collaboration of representatives from most of the large randomized, controlled trials of antihypertensive drug treatment. Its results are derived from centralized files of the baseline and follow-up data available for all patients enrolled in the trials.

The Trials

Our report is based on seven trials (5–7, 10–12, 16) (**Table 1**) in which both men and women were enrolled. The inclusion criteria for the trials in the INDANA project are discussed elsewhere (15). In summary, the steering group of the project made the following decisions: The data from the Australian trial (8) were not included in the analysis because separate outcomes are not available without censoring bias; the EWPHE trial (7) data were included only for the analysis of mortality end points (separate nonfatal outcomes are not available without censoring bias); and the data from HDFP (5) were considered in a sensitivity analysis (analysis was done with and without these data because of the originality of the trial design, which compared specific antihypertensive care systems with usual care). The data from the Veterans Administration and National Heart, Lung, and Blood Institute feasibility trial (17) are available in the INDANA database but have not yet been submitted to control and extraction procedures. Thus, these data were not used in our analysis. Because this trial has only a small weight in terms of patient-years and observed events, its exclusion is unlikely to change the results presented here.

Outcomes

According to the INDANA protocol, seven outcomes were analyzed: 1) fatal strokes; 2) fatal and nonfatal strokes, excluding transient ischemic attacks; 3) fatal coronary events (including sudden death, which was defined as unexpected and unexplained death occurring within a maximal interval of 24 hours after symptom onset); 4) fatal and nonfatal major coronary events (using criteria for major coronary heart disease obtained from patient histories in HDFP) (1); 5) cardiovascular-related mortality, including death from pulmonary thromboembolism; 6) major cardiovascular events (combining the second, fourth, and fifth outcomes and excluding such minor cardiovascular events as angina pectoris, intermittent claudication, or nonfatal congestive heart failure); and 7) total mortality.

Table 1. Main Characteristics of the Seven Antihypertensive Drug Trials That Enrolled Men and Women*

Trial (Reference)	Patients		Follow-up	Men	Age			Type of Trial	Inclusion Criteria	Mean Baseline Blood Pressure	First Study Treatment
	Treated	Control			Minimum	Maximum	Mean				
	n		*y*	%	← *y* →					*mm Hg*	
Hypertension in older persons											
EWPHE (7)	416	424	4.7	30	60		72	DB; PC	SBP 160–239 mm Hg and DBP 90–119 mm Hg	182/101	Thiazide diuretics
Coope and Warrender (16)	419	465	4.4	31	60	79	69	Open	SBP > 170 mm Hg or DBP 105–120 mm Hg	196/99	β-blocker
SHEP (11)	2365	2371	4.5	43	60		72	DB; PC	SBP 160–219 mm Hg and DBP < 90 mm Hg	170/77	Thiazide diuretics
STOP (12)	812	815	2.1	37	70	84	76	DB; PC	SBP 180–230 mm Hg and DBP >90 mm Hg or DBP 105–120 mm Hg	187/104	Thiazide diuretics or β-blocker
MRC65-74 (10)	2183	2213	5.8	42	65	74	70	SB; PC	SBP 160–209 mm Hg and DBP < 115 mm Hg	185/91	Thiazide diuretics or β-blocker
Mild to moderate hypertension in younger persons											
HDFP (5)	5485	5455	5.0	54	30	69	51	Open	DBP > 90 mm Hg	159/101	Thiazide diuretics
MRC35-64 (6)	8700	8654	4.9	52	35	64	52	SB; PC	SBP < 200 mm Hg and DBP 90–109 mm Hg	161/98	Thiazide diuretics or β-blocker

* DB = double-blind; DBP = diastolic blood pressure; EWPHE = European Working Party on High Blood Pressure in the Elderly; HDFP = Hypertension Detection and Follow-up Program; MRC35-64 = Medical Research Council trial of treatment of mild hypertension; MRC65-74 = Medical Research Council trial of treatment of hypertension in older adults; PC = placebo-controlled; SB = single-blind; SBP = systolic blood pressure; SHEP = Systolic Hypertension in the Elderly Program; STOP = Swedish Trial in Old Patients with Hypertension.

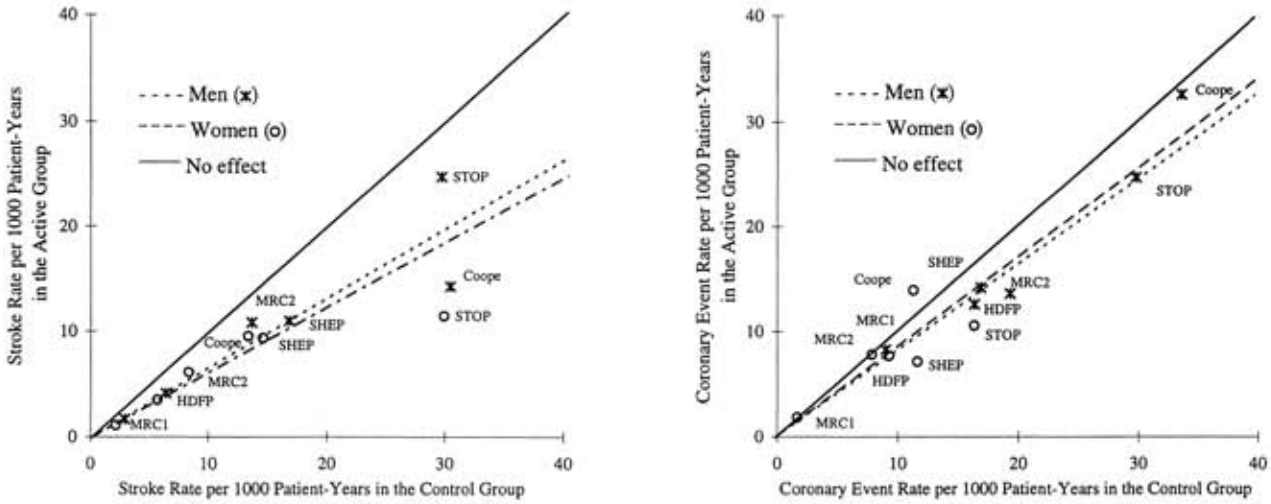

Figure 1. Effect of antihypertensive treatment on absolute risk for fatal and nonfatal stroke (*left*) and fatal and nonfatal coronary events (*right*). The points show subgroups in each trial by sex; the x-axis represents risk in the control group, and the y-axis represents risk in the treatment group. The risk is given as the rate for 1000 patient-years. The two dashed lines represent the odds ratios in women and men. Coope = Coope and Warrender (16); HDFP = Hypertension Detection and Follow-up Program (5); MRC1 = Medical Research Council trial of treatment of mild hypertension (6); MRC2 = Medical Research Council trial of treatment of hypertension in older adults (10); SHEP = Systolic Hypertension in the Elderly Program (11); STOP = Swedish Trial in Old Patients with Hypertension (12).

Statistical Analysis

Summarized data (number of patients and number of events) were extracted from the INDANA database by sex and by trial according to the intention-to-treat principle. For the group assigned to receive active treatment, the odds ratio compared with controls was estimated by sex for each outcome according to the Peto method (18). The odds ratio in women was compared with the odds ratio in men by determining whether the ratio was different from 1. This interaction between sex and treatment effect was checked after adjustment for the main baseline risk factors (age, baseline smoking habits, systolic blood pressure, serum cholesterol level, presence of diabetes, and history of stroke or myocardial infarction) in a multivariate logistic model (19) fitted by outcome.

For HDFP (5), we censored data at the date of the end of the trial intervention. Two deaths in the trial by Coope and Warrender (16) that were caused by pulmonary embolism were included with cardiovascular-related mortality in our analysis; one early cancer-related death in this trial was included in the analyses of total mortality because of the intention-to-treat principle.

To illustrate the difference in the treatment effect between men and women, we applied two graphical approaches to the second and fourth outcomes (all strokes and all coronary events). First, each trial was represented by sex in a treatment-effect graph (20) in which the x-axis is the risk observed in the control group (*Rc*) and the y-axis is the risk observed in the treated group (*Rt*) (**Figure 1**). The odds ratio line, with a slope equal to the odds ratio and a null intercept, indicates the treatment effect by sex. The principal diagonal of the plane $Rt \times Rc$ represents the absence of treatment effect ($Rt = Rc$; odds ratio, 1). The vertical distance between the odds ratio line and the principal diagonal indicates

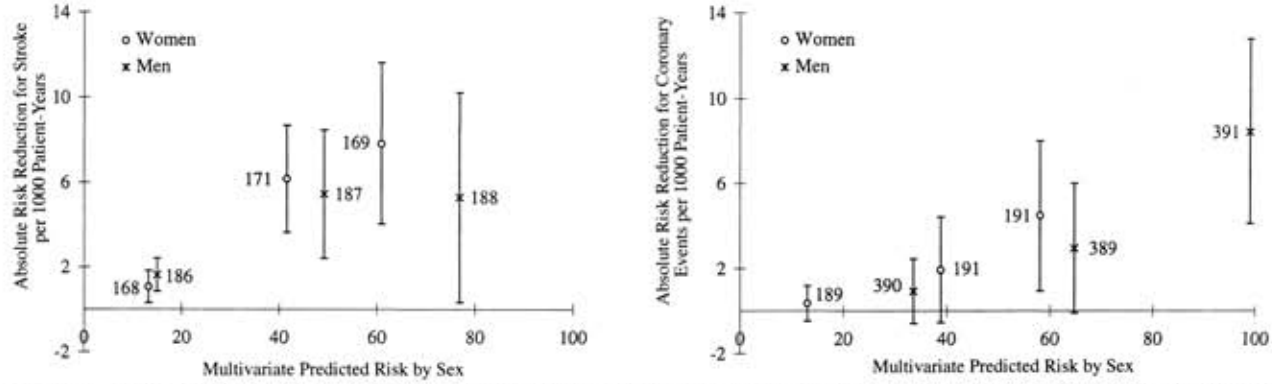

Figure 2. Absolute risk reduction of fatal and nonfatal stroke (*left*) and fatal and nonfatal coronary events (*right*) by untreated risk level and sex. The points show the absolute risk reduction on the y-axis with 95% CIs. The x-axis represents the predicted untreated risk. The number next to each point is the number of events observed by tertile. The predicted risk was obtained from a multivariate score established on the control group with the main cardiovascular risk factors: age, baseline smoking habits, blood pressure, serum cholesterol level, diabetes, and history of stroke or myocardial infarction.

Table 2. Main Cardiovascular Risk Factors by Sex*

Variable	Women†	Men‡
Age, *y*	59.3 ± 12.0	56.0 ± 11.6
Total serum cholesterol level, *mmol/L*	6.5 ± 1.2	6.1 ± 1.1
Systolic blood pressure, *mm Hg*	170.9 ± 20.9	162.6 ± 19.9
Diastolic blood pressure, *mm Hg*	95.6 ± 11.8	96.5 ± 10.4
Diabetes, %	4.2	3.7
History of stroke, %	1.3	1.3
History of myocardial infarction, %	2.6	4.3
Smoker, %	22.9	32.6

* Values in the first four rows are the mean ± SD.
† 10 399 patients receiving treatment and 10 403 controls.
‡ 9981 patients receiving treatment and 9994 controls.

the absolute risk reduction for a given untreated risk. Second, the absolute risk reduction attributable to treatment and its CI were computed by tertiles of individually predicted risk for each sex and were plotted against the average predicted risk in each tertile (**Figure 2**). The predicted risk was derived from individual scoring built on the results of a multivariate logistic model, including the major risk factors mentioned above. Tertiles were computed to contain similar numbers of events.

Meta-analysis computations were done using Easy-MA software (21); data management and logistic regression were done using SAS software (22).

Results

The key features of the seven trials are presented in **Table 1.** Five of the trials addressed hypertension in older persons, and two studied mild to moderate hypertension in younger persons. The drugs used in the trials were primarily thiazide diuretics, β-blockers, or both. The data for these seven trials contained in the INDANA database represent 97.5% of all existing data from all applicable trials in terms of patient-years of follow-up during the active phase of the trials. The combined trial data on risk factors by sex (**Table 2**) show that, on average, women were older; had a higher baseline cholesterol level, a higher systolic blood pressure, and a lower smoking rate; and less frequently had a history of myocardial infarction. Because these baseline characteristics were similar for the active treatment and control groups, these groups are combined in **Table 2.**

For each of the seven outcomes, **Table 3** shows the number of events in the active treatment and control groups that occurred in men and women, both within each trial and in all trials combined.

The exclusion of the HDFP data from the analysis changes neither the direction nor the magnitude of the odds ratio for either sex and does not affect the differences between men and women. These data are therefore included in the results presented. In **Table 4**, the combined odds ratios for all trials are shown separately for men and women; these odds ratios were estimated using a fixed-effects method. In women, odds ratios favoring treatment were statistically significant for strokes (both fatal and either fatal or nonfatal) and major cardiovas-

Table 3. Events by Trial and Sex*

Trial (Reference)	Patients		Patient-Years		Total Deaths		Cardiovascular-Related Deaths		All Strokes		Fatal Strokes	
	Active	Control	Active	Control	Active	Control	Active	Control	Active	Control	Active	Control
	← *n* →											
EWPHE (7)												
Women	287	299	1331	1453	92	104	50	63			17	21
Men	129	125	607	564	43	45	17	30			4	10
Coope and Warrender (16)												
Women	297	314	1364	1419	32	28	19	20	13	19	3	6
Men	122	151	491	657	28	42	16	30	7	20	1	9
SHEP (11)												
Women	1331	1359	5882	5941	98	120	43	62	55	87	8	9
Men	1034	1012	4375	4274	115	122	47	50	48	72	2	5
STOP (12)												
Women	510	509	1135	1103	21	30	9	20	13	33	1	10
Men	302	306	647	673	15	33	8	21	16	20	3	5
MRC65-74 (10)												
Women	1273	1287	7539	7541	118	135	72	65	46	63	18	17
Men	910	926	5073	5186	183	180	89	115	55	71	19	25
HDFP (5)												
Women	2524	2506	12 340	12 176	127	155	69	85	43	69	13	26
Men	2961	2949	14 298	14 076	223	266	126	155	59	90	16	26
MRC35-64 (6)												
Women	4177	4129	20 806	20 518	91	72	30	27	23	44	12	14
Men	4523	4525	22 202	22 274	157	181	104	112	37	65	6	13
All trials combined												
Women	10 399	10 403	50 397	50 151	579	644	292	342	193	315	72	103
Men	9981	9994	47 693	47 704	764	869	407	513	222	338	51	93

* EWPHE = European Working Party on High Blood Pressure in the Elderly; HDFP=Hypertension Detection and Follow-up Program; MRC35-64=Medical Research Council trial of treatment of mild hypertension; MRC65-74=Medical Research Council trial of treatment of hypertension in older adults; SHEP=Systolic Hypertension in the Elderly Program; STOP=Swedish Trial in Old Patients with Hypertension.

cular events but not for other outcomes. In men, odds ratios favoring treatment were statistically significant for all seven outcomes considered. No significant interaction was found between sex and treatment effect: The odds ratios between the treated and control groups did not differ between women and men, regardless of outcome. Adjustment for the major available baseline risk factors (including age, blood pressure, smoking habits, serum cholesterol level, presence of diabetes, and history of stroke or myocardial infarction) in a logistic regression model did not change this finding.

The graphical approaches illustrate the absence of interaction between sex and the size of the treatment effect for major coronary events and strokes. On the treatment effect graph (**Figure 1**), the size of the absolute risk reduction is indicated by the vertical distance between the odds ratio line and the principal diagonal for each sex. This size depends on the untreated risk, not on sex; for an untreated risk of 10 per 1000 patient-years, the absolute risk reduction in both women and men is approximately 1 for coronary events and 3 for strokes. For an untreated risk of 30, the absolute risk reduction in both women and men is approximately 3 for coronary events and 10 for strokes. This means that when the untreated risk is 10 per 1000 patient-years, the number of patients needed to treat over 1 year (the reciprocal of the absolute risk reduction) to avoid one coronary event is about 1000; the number needed to treat to avoid one stroke is about 300. The corresponding figures for an untreated risk of 30 per 1000 patient-years are about 300 and 100. These figures are the same in women and men.

The graph by tertile of predicted risk (**Figure 2**) shows that the size of the absolute risk reduction is the same in women and men whose untreated risk is similar and that the reduction increases with untreated risk. In the control group, the untreated risk distribution for stroke is similar in men and women; in men, the distribution for coronary events and the corresponding absolute risk reduction shifted to higher levels in men.

Table 3. ***Continued***

All Major Coronary Events		Fatal Coronary Events		Main Cardiovascular Events	
Active	Control	Active	Control	Active	Control
←		*n*			→
		10	12		
		2	13		
19	16	11	10	32	38
16	22	14	18	22	42
42	69	22	40	100	158
62	72	37	33	115	148
12	18	6	8	26	51
16	20	4	12	32	43
59	59	38	40	116	127
69	100	47	70	142	182
95	113	41	39	149	195
180	230	90	109	254	325
38	34	18	10	61	80
184	200	88	87	225	272
265	309	146	159	484	649
527	644	282	342	790	1012

Discussion

Our analysis was based on data from 7 of 15 trials (5–8, 10–12, 16, 17, 23–28) that compared antihypertensive drug interventions with placebo or no (or minimal) treatment and enrolled both men and women. It is unlikely, however, that the trials that have not been integrated into the INDANA database would change the results presented here: The analyzed data represent more than 97% of the patient-years of follow-up for these 15 trials.

We selected the outcomes on the basis of several criteria, including the availability of the outcomes, their homogeneity across trials, the reliability of their notification, and their clinical relevance. In particular, we did not use softer criteria, such as nonfatal heart failure, angina pectoris, or intermittent claudication, which may have been affected by antihypertensive drugs. Thus, the number of patients needed to treat to avoid an event may not represent all patients in whom treatment is beneficial. Rather, this number is specific for the considered outcomes.

The drugs used in the trials analyzed here were primarily thiazide diuretics, β-blockers, or both. We cannot extrapolate these results to other antihypertensive drugs without further research. Trials comparing drug classes are currently under way, and a prospectively planned review (29) of these trials should indicate whether our results are reproducible if drugs other than thiazide diuretics and β-blockers are used as first-line intervention.

In men, odds ratios favoring treatment were statistically significant for all outcomes considered. The fact that statistical significance for coronary events or total mortality was not reached in women may have a simple explanation: The underlying rate of these events was lower in women than in men, which means that the analyses of data in women had less statistical power. Indeed, the number of coronary events observed in women was roughly half that observed in men. In contrast, when the

Table 4. Estimate of Treatment Effect by Sex

Variable	Total Mortality	Cardiovascular-Related Death	Fatal Strokes	All Strokes	Fatal Coronary Events	All Major Coronary Events	Main Cardiovascular Events
Women							
Odds ratio (95% CI)	0.91 (0.81–1.01)	0.86 (0.74–1.01)	0.71 (0.53–0.96)	0.62 (0.52–0.73)	0.92 (0.74–1.16)	0.85 (0.72–1.01)	0.74 (0.66–0.83)
P value	0.094	0.068	0.03	<0.001	0.48	0.059	<0.001
Men							
Odds ratio (95% CI)	0.88 (0.80–0.97)	0.80 (0.70–0.91)	0.57 (0.41–0.78)	0.66 (0.56–0.78)	0.83 (0.71–0.97)	0.82 (0.73–0.92)	0.78 (0.71–0.86)
P value	0.013	<0.001	<0.001	<0.001	0.023	<0.001	<0.001
Interaction *P* value*	0.69	0.45	0.31	0.62	0.42	0.61	0.62

* The interaction *P* value defines the significance of the difference in odds ratio between women and men.

control groups of the seven trials are considered together, men and women had similar numbers of observed strokes and similar numbers of patient-years of follow-up (**Table 3**).

No evidence of interaction was found between sex and treatment effect in relative terms; this means that the odds ratios for treatment should be the same for men and women. However, the absolute risk reduction is not the same for women and men; as shown in the figures, this reduction depends on the untreated risk level. Both absolute risk reduction and its reciprocal number needed to treat are estimates that are more helpful for understanding the size of treatment benefit: When a clinician states that treatment prevents half the strokes, this half could be close to 0 and therefore practically negligible if the untreated risk is very low. In contrast, this effect could be clinically meaningful if the untreated risk exceeds a given threshold. This threshold is arbitrary, however, as is the definition of hypertension. Absolute risk reduction does not reflect only the proportionate treatment effect (for example, a 50% reduction in the rate of stroke); it also contains information on the untreated risk.

Our results are based on post hoc analyses; in none of the included trials was the comparison of the treatment effect size between men and women a main objective. It would not be correct, therefore, to conclude that treatment effect size does not differ whatsoever between men and women. We have shown only that the available data to date do not suggest such a difference.

Extrapolating the size of the treatment benefit by using predicted untreated risk is a way to individualize antihypertensive drug treatment (30, 31). However, the validity of such extrapolation requires that there be no interaction between baseline characteristics and the treatment effect in relative terms. It is impossible to be sure from the seven trials alone that no such interaction exists, but the available data do not support it.

Our meta-analysis includes almost all of the data from trials in which antihypertensive treatment was assessed in both sexes. It indicates that with treatment, odds ratios for cardiovascular risk are similar in women and men. However, the quantification of benefit in terms of absolute risk reduction shows that for women, the benefit is seen primarily for strokes, whereas in men treatment prevented as many coronary events as strokes. These findings suggest that the absolute benefit for the two main categories of cardiovascular events cannot be predicted across the sexes and that physicians need appropriate tools for predicting untreated risk in order to individualize antihypertensive and other preventive therapies.

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Socrates: "... the Greek physicians are quite right as far as they go ... but as you ought not to attempt to cure the eyes without the head, or the head without the body, so neither ought you attempt to cure the body without the soul. And this is the reason why the cure of many diseases is unknown to the physicians of Hellas, because they disregard the whole, which ought to be studied also, for the part can never be well until the whole is well."

Plato
"Charmides Dialogue"
Plato: The Collected Dialogues
Edith Hamilton and Huntington Cairs, eds.
Princeton, NJ: Princeton Univ Pr; 1961

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