Efficacy of Treating Hypertension in Women

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OBJECTIVE: **To assess whether the relative and absolute benefit of hypertension treatment in women varies with age or race.**

DESIGN: **Systematic review of studies from 1966 to 1998 using MEDLINE, reviews, and consultation with experts. Eleven randomized controlled trials of pharmacologic treatment of primary hypertension with cardiovascular morbidity and mortality outcomes were selected, with a pooled population of 23,000 women. Relative risks were combined for each end point to form a summary risk ratio using meta-analytic techniques based on a random-effects model. Summary risk ratios were converted to numbers needed to treat (NNTs). Data were dichotomized by age to approximate menopausal status (30 to 54 years, and 55 years and older), and by race (white and African American).**

MAIN RESULTS: **In women aged 55 years or older (90% white), hypertension treatment resulted in a 38% risk reduction in fatal and nonfatal cerebrovascular events (95% confidence interval [CI] 27%, 47%; 5-year NNT 78), a 25% reduction in fatal and nonfatal cardiovascular events (95% CI 17%, 33%; 5-year NNT 58), and a 17% reduction in cardiovascular mortality (95% CI 3%, 29%; 5-year NNT 282). In women aged 30 to 54 years (79% white), hypertension treatment resulted in a 41% risk reduction in fatal and nonfatal cerebrovascular events (95% CI 8%, 63%; 5-year NNT 264), and a 27% risk reduction in fatal and nonfatal cardiovascular events (95% CI 4%, 44%; 5-year NNT 259). Hypertension treatment in African-American women (mean age, 52 years) reduced the risk of fatal and nonfatal cerebrovascular events by 53% (95% CI 29%, 69%; 5-year NNT 39), fatal and nonfatal cardiovascular events by 45% (95% CI 18%, 63%; 5-year NNT 21), fatal and nonfatal coronary events by 33% (95% CI 6%, 52%; 5-year NNT 48), and all-cause mortality by 34% (95% CI 14%, 49%; 5-year NNT 32). Analyses in white women aged 30 to 54 years did not show any statistically significant treatment benefit or harm.**

CONCLUSIONS: **Hypertension treatment lowers the relative and absolute risk of cardiovascular morbidity and mortality in women aged 55 years and older and in African-American women of all ages. A greater effort should be made to increase awareness and treatment in these groups of women. Although relative risk reductions for cerebrovascular and cardiovascular events are similar for younger and older women, the NNT of younger women is at least 4 times higher. Decisions about treatment of hypertension in younger white women should be influenced by the individual patient's absolute risk of cardiovascular disease.**

KEY WORDS: **hypertension; women; treatment; age; race.**
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Treatment of hypertension in women is recommended to decrease the risk of cardiovascular disease.[1–5] The evidence for treatment benefit, however, is based primarily on combined results for men and women.[6–9] Recently the Individual Data Analysis of Antihypertensive intervention trials (INDANA) group assessed the benefit of hypertension treatment in women separately by pooling data for women participants from seven randomized controlled trials.[10] Results showed a significant 29% risk reduction in fatal cerebrovascular events, 38% risk reduction in nonfatal and fatal cerebrovascular events, and 26% risk reduction in cardiovascular events in women. The magnitude of risk reduction was similar to that in men, although in men the decreases in fatal and nonfatal coronary events and total mortality were also significant.

Although the INDANA study is the most complete quantitative review of hypertension treatment in women to date, data confirming a significant clinical benefit in younger women are lacking.[4,11,12] Subgroup analyses according to gender in the Medical Research Council (MRC)[13] and Hypertension Detection and Follow-up Program (HDFP)[14] trials, both with a mean population age of 51 years, suggested an increase in total mortality ranging from 2.5% to 26% among women treated for hypertension. In contrast, a subgroup analysis of men in the same trials showed significant risk reduction in mortality and cerebrovascular events.[15] Although these subgroup analyses in younger women have inadequate statistical power to allow a meaningful conclusion, the lack of a clear treatment benefit and the possibility of harm raise the question of whether treating hypertension in a group with low cardiovascular risk, such as young women, is clinically beneficial.

Subgroup analyses of African-American women from individual studies showed a trend toward benefit with hypertension treatment, but the statistical significance of the analyses was not published.[15–16] Data from randomized studies have not been pooled to determine a more stable risk estimate in African-American women treated for hypertension. Yet, the magnitude of treatment benefit is an important clinical issue because hypertension is a major health problem in African-American women. The prevalence of hypertension in African-American women (23%) is nearly double that in white women (12%).[17] The

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higher prevalence and earlier onset of hypertension in African-American women contribute to a more severe course and a higher incidence of cardiovascular morbidity and mortality at younger ages, including higher rates of stroke mortality, coronary disease mortality, and end-stage renal disease, compared with nonhypertensives.[18–20]

We used meta-analytic techniques to combine data from randomized controlled trials to determine whether the benefit of treating hypertension in women differed significantly between younger versus older women, and between white versus African-American women. We also calculated the number needed to treat (NNT) according to age and race to assess the absolute clinical benefit of treating hypertension in these subgroups of women.

METHODS

Data Acquisition and Abstraction

We performed a literature search of studies published between 1966 and September 1998 using the MEDLINE computer database and the following MeSH terms: *hypertension, Women,* and *Mortality* or *Stroke,* and *Randomized controlled trial* and *English.* Other studies were identified from review articles and consultation with experts. In the case of multiple publications from a single study, we used the most recent publication.

Retrieved articles were selected if they met all of the following criteria: (1) the study was a randomized controlled trial; (2) the population included more than 100 women with essential hypertension; (3) hypertension was defined as diastolic pressure >89 mm Hg, systolic pressure >139 mm Hg, or isolated systolic pressure >159 mm Hg with <90 mm Hg diastolic pressure; (4) an intervention group received treatment with either a single or multiple pharmacologic agents; (5) a control group received either placebo or standard care; (6) individual patient end points were available according to gender or race or both; and (7) study outcomes included cardiovascular morbidity and mortality outcomes.

Study outcomes were defined similarly to previous hypertension meta-analyses,[8,10] according to cardiovascular morbidity and mortality events: (1) fatal cerebrovascular events; (2) combined fatal and nonfatal cerebrovascular events, excluding transient ischemic attacks; (3) fatal coronary events, defined as either myocardial infarction or sudden cardiac death; (4) combined fatal coronary events and nonfatal myocardial infarctions; (5) combined fatal cardiovascular events, including category 1 and 3 above and fatal pulmonary embolus and ruptured aortic aneurysm; (6) combined fatal and nonfatal cardiovascular events (nonfatal cerebrovascular accidents and nonfatal myocardial infarctions); and (7) death from any cause. A cerebrovascular event was defined as a persistent neurologic deficit lasting 24 hours or more with or without verification by radiologic imaging, and myocardial infarction was defined as persistent ischemic electrocardiogram changes, or verified enzyme elevation. The definition of major outcomes of cardiovascular morbidity and mortality were similar for each study, except for the Australian study,[21] which reported three nonfatal outcomes that differed from the other trials (transient ischemic attacks, congestive heart failure, and evidence of hypertensive end-organ damage), and the HDFP,[14] which measured all-cause mortality as a primary outcome and assessed cause-specific outcomes according to coding on death certificates and retrospective patient interviews. Only fatal end points from the Australian study (cerebrovascular events, coronary events, and cardiovascular mortality) were incorporated into the meta-analysis. For HDFP, all results were incorporated into the meta-analysis.

Study eligibility was assessed by two reviewers according to an abstraction form designed prior to the literature search. Results for women participants in studies were available from publications,[13,22] primary authors,[23–25] and the INDANA hypertension database,[10,26] which had independently collected individual patient outcome data from two of the published studies,[13,22] as well as six other eligible studies.[14,16,21,27–29] Only five studies clearly specified the race of individual patients.[14,16,23–25] All women in the Cardiovascular Study in the Elderly (CASTEL) and Systolic Hypertension in Europe (Syst-Eur) studies were white (Dr. E. Casiglia and Dr. J.A. Staessen, personal communication).[24,25] The other three studies are from the United States, and have only two race categories, "white" and "black." The other six studies did not designate race, but were conducted in geographic areas of white predominance. Thus, the race subgroups in our review will be designated as African American and "white," the latter of which encompasses patients of any other unspecified race included in the studies.

Data Synthesis

Analysis of baseline characteristics and multivariate logistic regressions were conducted in collaboration with INDANA. Percentages and means for baseline characteristics were calculated by combining individual patient data from all studies that met inclusion criteria except for the Systolic Hypertension in the Elderly (SHEP) pilot, CASTEL, and Syst-Eur, from which baseline data were not available.

To estimate the benefit of treating hypertension in women, we performed a meta-analysis using a DerSimion Laird (DL) random-effects model. Relative risks were calculated for each study and then combined to calculate a summary risk ratio (RR) and 95% confidence interval (CI) for each cardiovascular outcome. Summary estimates were calculated based on age (30–54 years vs 55 years and older) and race (white vs African American) in the same pooled population of women. We dichotomized the data at age 55 because by this age, 90% of women are menopausal,[30,31] after which cardiovascular risk begins to rise.[32] A χ^2 test for homogeneity was performed for all

summary estimates; p values $\leq .1$ were considered statistically significant.

Summary risk ratios (RR_{DL}) were converted to estimates of NNT, which is the number of patients who must be treated to prevent one adverse outcome.[33–36] The NNT was determined by calculating the absolute risk and then using the following formulas where $p'(C)$ is a pooled estimate for the proportion of events in the control group and is calculated using the proportion of events in the control group $p(C)$, variance $(p(C))$, total number of control patients $n(C)$, and weight from individual studies.

$$\text{Variance}(p(C)) = (p(C) * (1 - p(C)))/(n(C)$$
$$\text{Weight} = 1/\text{var}(p(C))$$
$$p'(C) = \text{sum}(w * p(C))/\text{sum}(w)$$

The risk difference, or absolute risk for the pooled estimate, is obtained using

$$\text{Absolute Risk} = p'(C) * (RR_{DL}) - p'(C)$$
$$\text{NNT} = 1/(\text{Absolute Risk})$$

We standardized the NNT to 5 years, as most studies had a 5-year follow-up.

$$\text{Standard NTT} = \text{NNT}\ (\text{Length of follow-up}/\text{Standard years})$$

The pooled length of follow-up was weighted by dividing the sum of patient years from each study by the total number of women in each subgroup. Thus, to standardize to a 5-year NNT, if the pooled length of follow-up was 4.3 years, we multiplied the calculated NNT by (4.3/5).

To test the robustness of our results for younger and older women, we conducted a multivariate analysis with a logistic regression model using pooled data with adjustment for differences in the following baseline characteristics: age, systolic and diastolic hypertension levels, cholesterol level, smoking status, diabetes mellitus, and history of prior myocardial infarction or cerebrovascular accident. A multivariate analysis was also performed to test the robustness of our results according to race adjusting for the above characteristics. P levels were calculated for interactions between age group and treatment in the age analysis and between race and treatment in the race analysis.

RESULTS

Through our MEDLINE search, we retrieved 270 articles. Seven more articles[21,37–42] were found from references in review articles. Of the 277 eligible articles, 44 were multiple publications from the same studies. The other major reasons for study exclusion are shown in Table 1. Thirty-four randomized controlled studies of treatment for essential hypertension were identified. After applying inclusion criteria, only 11 studies remained eligible.[13,14,16,21–25,27–29] Of the 23 other studies, 7 studies included no women,[37,40–45] and 5 studies included fewer than 100 women.[38,39,46–48] The other 11 randomized controlled trials with cardiovascular outcomes were not included because the studies were currently ongoing,[49–53] data were unattainable from primary authors,[54] or two treatment groups were compared, rather than comparing a treatment group to a placebo or usual care group.[55–59]

Eligible studies are summarized in Table 2. Studies recruited women from 30 to 98 years old, with the mean age of women across trials ranging from 50.4 to 75 years. Mean follow-up of studies ranged from 2 to 12 years. Each study used a diuretic or β-blocker as first-line therapy, except for the CASTEL study,[24] which allowed clonidine or nifedipine, and the Syst-Eur study,[25] which used nitrendipine. Table 3 shows the number of women from each study dichotomized by age and race. There were approximately 8,500 women aged 30 to 54 years, and 17,600 women aged 55 years and older. When the same pooled group of women were dichotomized by race, there were 23,000 white women and 3,200 African-American women.

Table 4 summarizes pooled baseline characteristics of control and treated groups by age and race. Data on baseline characteristics were not available from CASTEL, Syst-Eur, and SHEP pilot studies, and information on other cardiovascular risk factors, such as left ventricular hypertrophy or obesity, was not collected for all of the studies. Among women aged 30 to 54 years (79% white), the control group had a slightly higher percentage of smokers than the treated group (33% vs 31%, $p = .025$). Among women aged 55 years and older (90% white), there were no significant differences in mean age, systolic and diastolic blood pressure, total cholesterol level, or prevalence of smoking, diabetes, and history of cerebrovascular accidents or coronary events. When baseline characteristics of the women were examined according to race, white women treated for hypertension had a slightly higher percentage of prior myocardial infarction than the control group (1.7% vs 1.3%, $p = .02$). In comparison with white women, African-American women were younger (mean age, 52 years), with a higher percentage who were smokers, diabetics, or had a history of prior myocardial infarction or cerebrovascular accident. There were no significant

Table 1. Reason for Exclusion of Studies

Primary Reason for Exclusion	Number of Reports
Not a randomized controlled trial	18
No women included	7
Fewer than 100 women in study	5
Not essential hypertension	91
No pharmacologic intervention/ no control	29
No cardiovascular morbidity or mortality outcomes	66
Data still in collection phase	5
No data available by gender and age	1
Multiple publications	44
Total	**266**

Table 2. Overview of Hypertension Randomized Controlled Trials

Study*	Year	Women, *n*	Mean Age, years	Follow-up, years	First Line Treatments
HDFP[14]	1978	5,030	52.3	4.9	Chlorthalidone
Australian[21]	1980	1,456	50.4	2.9	Chlorothiazide
MRC[13]	1985	8,306	51	5	Bendrofluazide or propranolol
EWPHE[27]	1985	586	72	4.6	Hydrochlorothiazide/triamterene
Coope[28]	1986	611	68	4.5	Atenolol
SHEP pilot[23]	1989	349	72	2.8	Chlorthalidone
SHEP[16]	1991	2,690	72	4.4	Chlorthalidone
STOP[29]	1991	1,019	75	2.2	Hydrochlorothiazide/amiloride, Metoprolol, pindolol, or atenolol
MRC elderly[22]	1992	2,560	70	5.9	Hydrochlorothiazide/amiloride or atenolol
CASTEL[24]	1994	424	74	12	Clonidine or nifedipine
Syst-Eur[25]	1997	3,138	70.5	2	Nitrendipine

**HDFP indicates Hypertension Detection and Follow-up Program; MRC, Medical Research Council; EWPHE, European Working Party on High Blood Pressure in the Elderly; SHEP, Systolic Hypertension in the Elderly Program; STOP, Swedish Trial in Old Patients with Hypertension; CASTEL, Cardiovascular Study in the Elderly; Syst-Eur, Systolic Hypertension in Europe.*

differences in baseline characteristics between the treated and control groups of African-American women.

The summary relative risk estimates according to major cardiovascular events are shown according to age in Figures 1 and 2, and according to race in Figures 3 and 4, with vertical lines delineating the 95% CI. All combined results were found to be homogeneous ($p > .1$). In women aged 30 to 54 years treated for hypertension ($n = 8,565$), there was a statistically significant reduction in fatal and nonfatal cerebrovascular events (RR 0.59; 95% CI 0.37, 0.92) and fatal and nonfatal cardiovascular events (RR 0.73; 95% CI 0.56, 0.96) (Fig. 1). There was no significant reduction or increase in coronary morbidity or mortality, cardiovascular mortality, or all-cause mortality outcomes with hypertension treatment.

Figure 2 shows the summary estimates for cardiovascular outcomes in women aged 55 years and older ($n = 17,604$). Hypertension treatment resulted in a significant risk reduction in fatal and nonfatal cerebrovascular accidents (RR 0.62; 95% CI 0.53, 0.73) and fatal and nonfatal cardiovascular events (RR 0.75; 95% CI 0.67, 0.83). In addition, women aged 55 years and older treated for hypertension had a risk reduction in fatal cardiovascular events (RR 0.83; 95% CI 0.71, 0.97) and a reduction that bordered on significance for all-cause mortality (RR 0.89; 95% CI 0.80, 1.0). The summary estimates for coronary events were not statistically significant.

Figures 3 and 4 show the summary estimates for cardiovascular outcomes according to race. Summary estimates in white women ($n = 22,963$) were significant for fatal and nonfatal cerebrovascular events (RR 0.65; 95% CI 0.55, 0.77) and for fatal and nonfatal cardiovascular events (RR 0.78; 95% CI 0.7, 0.86). However, hypertension treatment in white women of all ages did not demonstrate a

Table 3. Number of Women in Randomized Controlled Studies According to Age and Race

	Women 30–54 Years		Women ≥ 55 Years		White Women		African-American Women	
Study*	Control	Treated	Control	Treated	Control	Treated	Control	Treated
HDFP[14]	1,568	1,540	938	984	1,197	1,133	1,356	1,344
Australian[21]	416	445	295	300	711	745		
MRC[13]	2,277	2,319	1,852	1,858	4,129	4,177		
EWPHE[27]			299	287	299	287		
Coope[28]			314	297	314	297		
SHEP pilot[23]			70	279	54	229	16	50
SHEP[16]			1,359	1,331	1,130	1,120	229	211
STOP[29]			509	510	509	510		
MRC elderly[22]			1,287	1,273	1,287	1,273		
CASTEL[24]			192	232	192	232		
Syst-Eur[25]			1,520	1,618	1,520	1,618		
Total	**4,261**	**4,304**	**8,635**	**8,969**	**11,342**	**11,621**	**1,601**	**1,605**

**HDFP indicates Hypertension Detection and Follow-up Program; MRC, Medical Research Council; EWPHE, European Working Party on High Blood Pressure in the Elderly; SHEP, Systolic Hypertension in the Elderly Program; STOP, Swedish Trial in Old Patients with Hypertension; CASTEL, Cardiovascular Study in the Elderly; Syst-Eur, Systolic Hypertension in Europe.*

Table 4. Baseline Characteristics of Women in the Pooled Population*

	Women 30–54 Years		Women ≥ 55 Years		White Women		African-American Women	
Baseline Characteristic†	Control	Treated	Control	Treated	Control	Treated	Control	Treated
Age, mean years	46.53	46.6	66.8	66.8	60.0	60.1	52.7	53.2
Baseline SBP	159.45	159.36	176.5	177	170.8	171.1	164.9	164.5
Baseline DBP	99.66	99.72	93.1	93.4	95.0	95.2	99.3	99.4
Baseline cholesterol	6.181	6.189	6.708	6.74	6.57	6.59	6.1	6.1
Smoker, %	33	31	17	18	21	21	33.6	34.4
Diabetes, %	3	3	5	5	2.7	2.7	11.1	9.3
History of CVA, %	1	1	1	2	0.8	0.9	2.5	2.9
History of MI, %	2	3	2	3	1.3	1.7	7	7.7

** Does not include data on patients from SHEP pilot, CASTEL, or Syst-Eur.*

† SBP indicates systolic blood pressure; DBP, diastolic blood pressure; CVA, cerebrovascular accident; MI, myocardial infarction.

reduction in coronary morbidity or mortality, cardiovascular mortality, or all-cause mortality. In comparison, hypertension treatment in African-American women (n = 3,206) resulted in substantial risk reduction in fatal and nonfatal cerebrovascular outcomes (RR 0.47; 95% CI 0.31, 0.71), fatal and nonfatal coronary events (RR 0.67; 95% CI 0.48, 0.94), fatal cardiovascular events (RR 0.65; 95% CI 0.45, 0.95), fatal and nonfatal cardiovascular events (RR 0.55; 95% CI 0.37, 0.82), and all-cause mortality (RR 0.66; 95% CI 0.51, 0.86).

When data were analyzed for white women aged 30 to 54 years (n = 6,731), there were no statistically significant

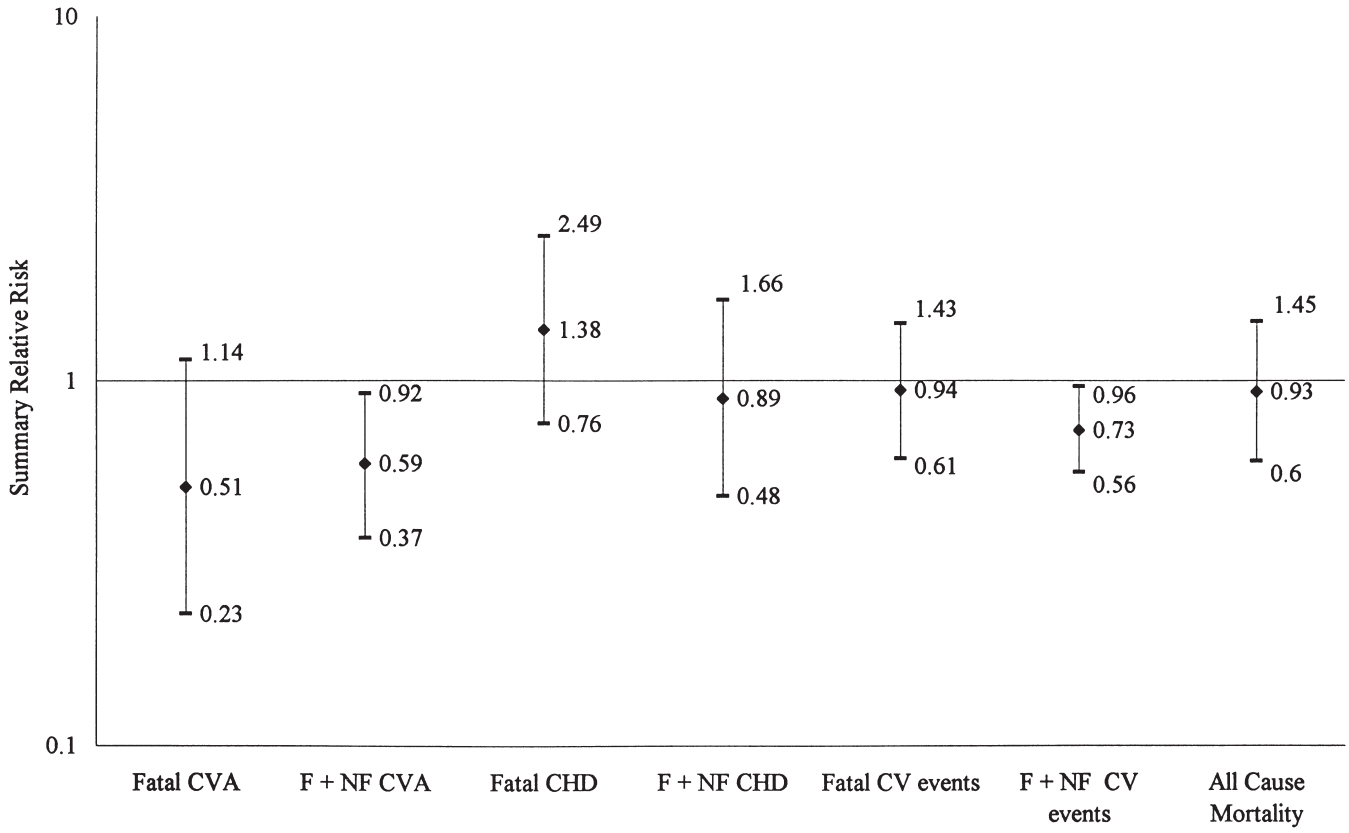

FIGURE 1. Summary estimates for major cardiovascular outcomes in women aged < 55 years treated for hypertension. Fatal CVA indicates fatal cerebrovascular accident; F + NF CVA, combined fatal and nonfatal cerebrovascular accidents; Fatal CHD, coronary heart disease events, including fatal myocardial infarction and sudden cardiac death; F + NF CHD, combined fatal CHD and nonfatal myocardial infarction; Fatal CV events, fatal cardiovascular events, including fatal CVA and fatal CHD, and fatal pulmonary embolus, aortic dissection, or aneurysmal rupture; F + NF CV events, combined fatal cardiovascular events, nonfatal cerebrovascular accidents, and nonfatal myocardial events.

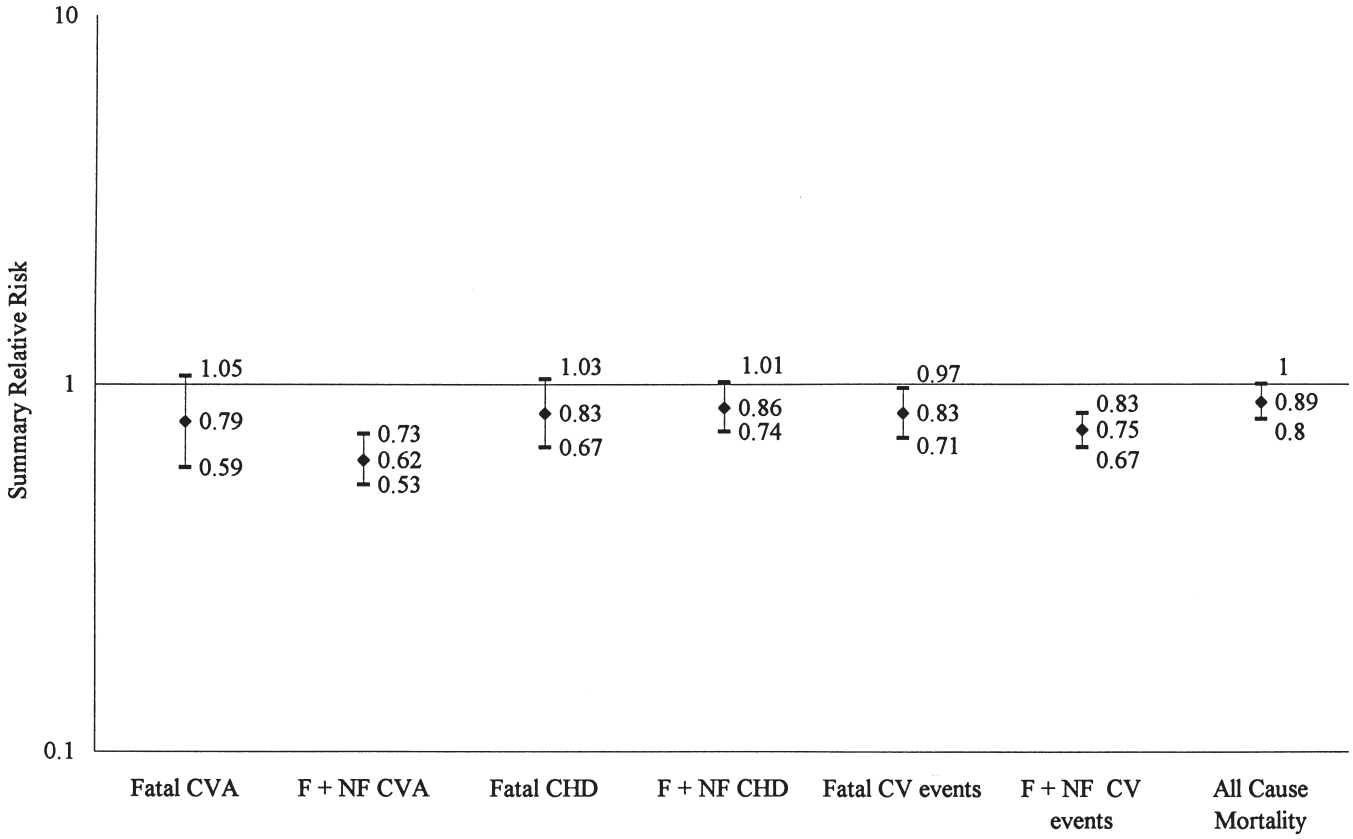

FIGURE 2. Summary estimates for major cardiovascular outcomes in women aged ≥ 55 years treated for hypertension. Abbreviations are explained in the legend to Figure 1.

reductions in cardiovascular morbidity or mortality, although the trends were similar to the results for all women aged 30 to 54 years. For fatal and nonfatal cerebrovascular events, the RR was 0.62 (95% CI 0.24, 1.59); for combined fatal and nonfatal coronary events, the RR was 1.4 (95% CI 0.62, 3.16); for combined fatal and nonfatal cardiovascular events, the RR was 0.74 (95% CI 0.51, 1.08); and for all-cause mortality, the RR was 1.08 (95% CI 0.73, 1.58).

The 5-year NNT values by age and race are shown in Table 5. In women aged 55 years and older, the 5-year NNT was 78 to prevent a fatal or nonfatal cerebrovascular event compared with 264 in women aged 30 to 54 years. For combined fatal and nonfatal cardiovascular events, older women had a 5-year NNT of 58 versus 259 in women aged 30 to 54 years. In the race analysis, 39 African-American women needed to be treated to prevent fatal or nonfatal cerebrovascular events, 48 women for fatal and nonfatal coronary events, 98 women for fatal cardiovascular events, 21 women for fatal and nonfatal cardiovascular events, and 32 women for all-cause mortality. For white women, the 5-year NNT for fatal and nonfatal cerebrovascular events was 178 women, and for fatal and nonfatal cardiovascular events, 158 women. For white women 30 to 54 years old, NNTs could not be calculated because summary estimates were not statistically significant.

A multivariate pooled analysis adjusting for baseline age, systolic and diastolic blood pressure, cholesterol levels, smoking status, diabetes mellitus, and history of myocardial infarction or cerebrovascular accident yielded odds ratios (Table 6) similar to the summary relative risk estimates shown in Figures 1 to 4. After adjusting for baseline characteristics, there were no significant interactions in the treatment effect between age groups (30 to 54 years vs 55 years and older) for any cardiovascular outcome. In contrast, in the race analysis, after adjustment for baseline characteristics, there was a significant difference between groups. Compared with white women, African-American women treated for hypertension had a greater risk reduction in fatal cardiovascular events (p = .05), fatal and nonfatal cardiovascular events (p = .04), and all-cause mortality (p = .003).

DISCUSSION

Case-control and cohort studies have consistently shown that diastolic and isolated systolic hypertension are risk factors for cardiovascular disease in women.[60–63] Furthermore, combined data from women in randomized controlled trials have shown that treating hypertension in women reduces the risk of fatal and nonfatal cerebrovascular and cardiovascular events.[10] Our study adds to this

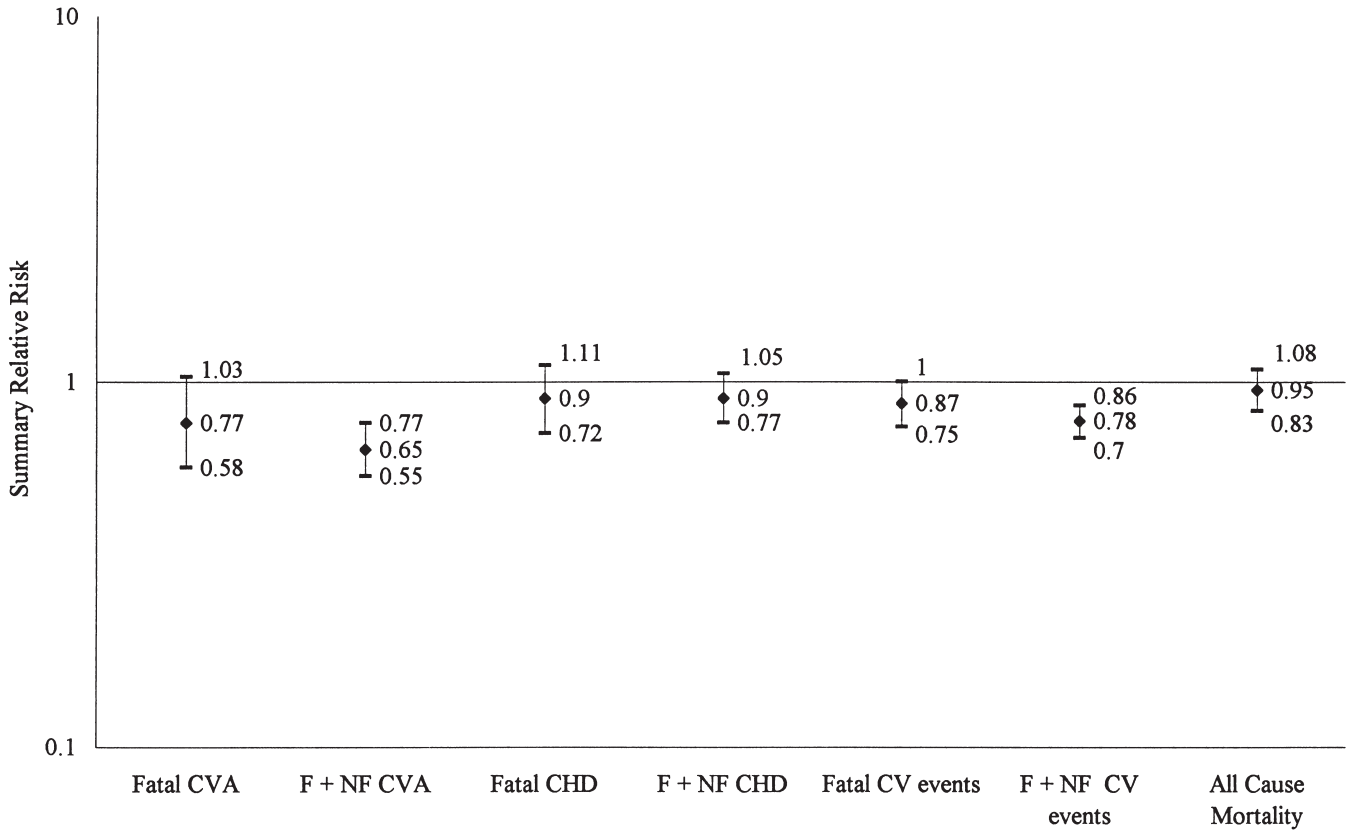

FIGURE 3. Summary estimates for major cardiovascular outcomes in white women treated for hypertension. Abbreviations are explained in the legend to Figure 1.

body of knowledge by quantitating the treatment benefit in women according to age and race. Our results demonstrate a significant relative risk reduction in cardiovascular outcomes in both younger and older women, and both white and African-American women. African-American women had the greatest magnitude of relative risk reduction in cardiovascular outcomes. We also found that the greatest absolute benefit occurred in African-American women and women aged 55 years and older. In comparison, younger white women, who have a lower prevalence of cardiovascular disease, had 5-year NNTs 3 to 4 times higher than those of older women.

Our results affirm that hypertension treatment markedly decreases the risk of cerebrovascular and cardiovascular morbidity and mortality in women aged 55 years and older. By this age, 90% of women are postmenopausal with cardiovascular risk approaching the level of age-matched men.[30–31] Although results for men and women combined demonstrated a reduction in coronary events,[7,8,64,65] we did not observe a significant coronary risk reduction in older women. As the confidence intervals for the summary estimate for coronary events were wide, the numbers may have been inadequate to provide the statistical power to demonstrate a significant reduction in coronary death.

For cerebrovascular and cardiovascular outcomes, our group of older women had similar relative risk reductions but slightly higher 5-year NNTs, compared with other studies in elderly hypertensive men and women.[8,25,64,65] For instance, in all cardiovascular events, the 5-year NNT was 18 in a meta-analysis of elderly hypertensive men and women[8] and was 18.5 in the Syst-Eur randomized trial of elderly hypertensives,[25] compared with 58 in the older women in our study. Likewise, for all cerebrovascular events, the 5-year NNT was 43 for elderly men and women[8] and 34.5 in Syst-Eur,[25] compared with 78 in the older women in our study. The difference in magnitude of benefit may, in part, be due to a lower mean age in our pooled older women (mean age, 66 years),[8] compared with the elderly population in the meta-analysis (mean age, 72 years) and in Syst-Eur (mean age, 70.2 years).[25] Besides a lower mean age, our pooled population of older women also had lower rates of comorbidities, such as prior myocardial infarction, cerebrovascular accidents, or diabetes. Comparatively, in the Syst-Eur study alone, 30% of the enrolled population had a history of cardiovascular complications and, thus, a higher baseline risk of a repeated cardiovascular event. Thus, our 5-year NNT values are best applied to women in the community with mild hypertension.

Age subgroup analyses from INDANA and Syst-Eur suggest an upper limit to the mortality treatment benefit for hypertension.[66,67] These studies did not find a mortality benefit with hypertension treatment in men and

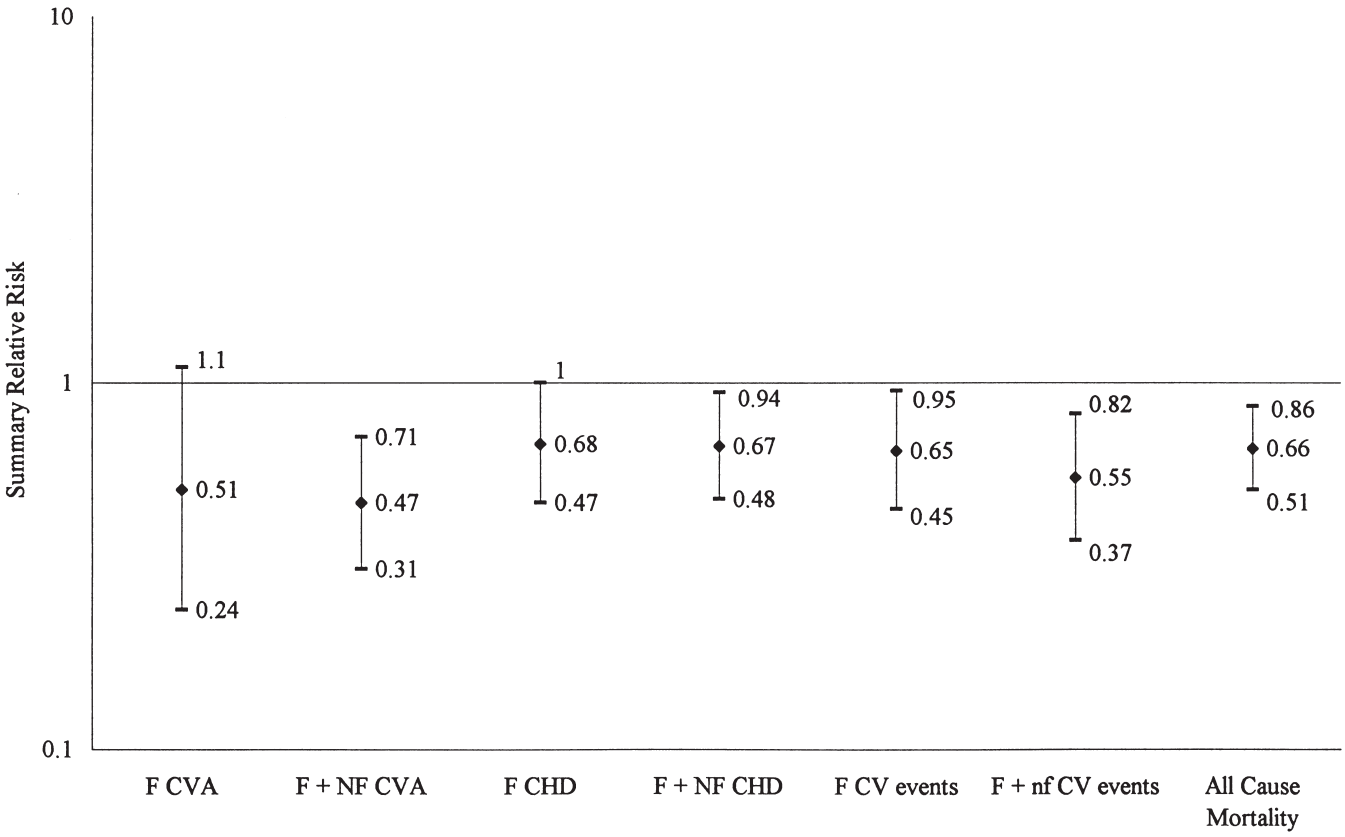

FIGURE 4. Summary estimates for major cardiovascular outcomes in African-American women treated for hypertension. Abbreviations are explained in the legend to Figure 1.

women beyond the age of 80 years. There was, however, significant risk reduction in cardiovascular and cerebrovascular morbidity in both studies. In our group of older women (mean age, 66 years), the relative risk reduction in cardiovascular mortality was statistically significant, and the risk reduction of all-cause mortality bordered on statistical significance. Unfortunately, we lacked the power to analyze results by decade of age to determine a specific age threshold above which hypertension treatment no longer affects mortality.

Our study is the first to combine data from randomized controlled trials to quantitate the benefit of treating hypertension in African-American women. Our results show a substantial benefit in African-American women treated for hypertension in the outcomes of cerebrovascular events, coronary events, cardiovascular mortality,

Table 5. Summary Relative Risk Estimates and 5-year number needed to treat by Age*

Outcome	Women 30–54 Years (n = 8,565)	Women ≥ 55 Years (n = 17,604)	White Women (n = 22,963)	African-American Women (n = 3,206)
Fatal CVA	NA	NA	NA	NA
F + NF CVA	264	78	178	39
Fatal CHD	NA	NA	NA	98
F + NF CHD	NA	NA	NA	48
Fatal CV events	NA	282	NA	98
F + NF CV events	259	58	158	21
All-cause mortality	NA	183	NA	32

**NA indicates not applicable—summary estimate with insignificant* p *value; Fatal CVA, Fatal cerbrovascular accident; F + NF CVA, combined fatal and nonfatal cerbrovascular accidents; Fatal CHD, coronary heart disease events, including fatal myocardial infarction and sudden cardiac death; F + NF CHD, combined fatal CHD and nonfatal myocardial infarction; Fatal CV events, fatal cardiovascular events, including fatal CVA and fatal CHD, and fatal pulmonary embolus, aortic dissection, or aneurysmal rupture; F + NF CV events, combined fatal CV events, and nonfatal cerbrovascular accidents, and nonfatal myocardial infarction.*

and all-cause mortality. Despite a mean age of 52 years, African-American women in our study had an absolute benefit comparable to elderly men and women with a mean age of 72 years treated for hypertension.[8] Because the treatment benefit appeared to extend to both younger and older African-American women, we recommend that African-American women with hypertension be treated irrespective of their age.

The treatment benefit stemmed, in part, from the higher absolute risk for cardiovascular disease in the pooled African-American women compared with white women (Table 4). However, even after adjusting for differences in baseline characteristics, African-American women treated for hypertension had a significantly greater relative risk reduction than white women in cardiovascular and mortality outcomes (Table 6). The reasons for a larger hypertension treatment benefit among the African-American women are unclear, but may be related to a higher inherent cardiovascular risk even after adjustment for baseline characteristics, a better response to treatment, or both.

As 85% of the African-American women were from the HDFP study alone,[14] the greater treatment benefit may also have stemmed from nondrug interventions afforded to the treatment arm of the HDFP study, such as greater access to care. A unique aspect of the HDFP design was that patients were not randomized to simple treatment and placebo groups, but to "stepped care" and "referred care" groups. The stepped care patients were treated according to a formal plan of "steps," which added medications as necessary to maintain blood pressure control, while the referred care group was released to the care of their individual doctors for "usual care" of hypertension treatment. The stepped care medication plan achieved higher rates of blood pressure control compared with the referred care group (68% vs 44%), possibly due to additional benefits given to the stepped care group, including measures to improve compliance such as pill counts, shorter appointment waiting times, formal counseling on other cardiovascular risk factors, and subsidized medications, laboratory tests, and transportation. The greater access to care for the stepped care patients also may have improved overall health status and contributed to improved cardiovascular outcomes. On the other hand, since the HDFP study had no true placebo group, the true size of the hypertension treatment effect was blunted by the large numbers of referred care patients on medication (60% of the African-American women on medication by year 5, with 44% at goal blood pressure).[15] Thus, the treatment benefit with hypertension treatment may be even greater than reported in our study.

Despite similar relative risk reductions in cardiovascular and cerebrovascular outcomes in women aged 30 to 54 years compared to with women over 55 years, the 5-year NNTs are 3 to 4 times higher in the younger women, reflecting their lower cardiovascular risk.[35,68,69] Undoubtedly, the significant relative risk reductions seen in cerebrovascular and cardiovascular outcomes in women aged 30 to 54 years are partially driven by the African-American women, who constituted 21% of the younger subgroup of women. Unfortunately, there were not enough events in white women aged 30 to 54 years to obtain a stable summary risk estimate. Thus, in treatment of hypertension in younger white women, our results support neither benefit nor harm, as suggested by subgroup analyses of white women in the MRC and HDFP studies. However, a true treatment benefit may have been blunted in younger white women by two factors: the partial treatment of control groups and the low cardiovascular risk status of young women enrolled in the studies. In the MRC and Australian studies, 10% to 12% of control patients received medication; and in the HDFP study, 64% of referred case patients received medication. However, a large absolute benefit from hypertension treatment was observed among older women and African-American women, who had similar rates of hypertension treatment in control groups. Thus, the higher NNTs in younger women in our results probably reflect a lower prevalence of cardiovascular disease, not an underestimation of treatment effect from contamination of the control group. Also, the three

Table 6. Multivariate Analysis Results: Testing for Interaction Between Age and Race and Treatment Status*

	Age Analysis Relative Risk (95% Confidence Interval)			Race Analysis Relative Risk (95% Confidence Interval)		
Outcome†	Women 30–54 Years	Women ≥ 55 Years	*p* Value‡	White Women	African-American Women	*p* Value‡
Fatal CVA	0.50 (0.21, 4.53)	0.71 (0.51, 0.98)	.46	0.72 (0.52, 1.01)	0.48 (0.23, 1.04)	.35
F + NF CVA	0.58 (0.36, 0.67)	0.62 (0.50, 0.76)	.82	0.65 (0.52, 0.80)	0.47 (0.52, 0.74)	.24
Fatal CHD	1.47 (0.78, 4.76)	0.84 (0.65, 1.08)	.11	0.95 (0.73, 1.23)	0.71 (0.40, 1.25)	.44
F + NF CHD	0.80 (0.56, 2.86)	0.82 (0.67, 1.01)	.90	0.88 (0.72, 1.08)	0.61 (0.42, 0.89)	.12
Fatal CV events	0.94 (0.60, 3.48)	0.84 (0.69, 1.01)	.63	0.92 (0.77, 1.12)	0.57 (0.38, 0.86)	.05
F + NF CV events	0.73 (0.54, 0.97)	0.71 (0.62, 0.82)	.89	0.76 (0.66, 0.87)	0.54 (0.40, 0.72)	.04
All-cause mortality	0.92 (0.68, 2.79)	0.89 (0.77, 1.02)	.84	0.98 (0.85, 1.13)	0.59 (0.44, 0.80)	.003

**Adjusted for age, baseline systolic and diastolic blood pressure, cholesterol level, smoking status, diabetes mellitus, history of myocardial infarction or cerebrovascular accident.*

† *Abbreviations are explained in the first footnote to Table 5.*

‡ *For interaction between groups.*

studies with women under 55 years of age recruited people through community screening and excluded many with significant systemic disease,[13,14,21] so the NNT calculated for women aged 30 to 54 years in our study pertains to a relatively healthy population of younger women.

The higher NNT to prevent a cardiovascular event in younger white women results in higher costs per event prevented than treating older women or African-American women. In general, $50,000 per year of life gained is considered an accepted cost for a medical intervention. One cost analysis of hypertension treatment based on a meta-analysis of hypertension trials estimates a *cost* of $229,000 per life-year gained for treating a 40-year-old hypertensive woman, compared with a *savings* of $161,000 to treat a 70-year-old woman with hypertension.[70,71] These cost analyses did not consider race.

The data for white women aged 30 to 54 years is not as convincing as those for older women or African-American women; risk stratification of younger white women with hypertension would help to identify the younger women who may benefit most from treatment.[35,68,72,73] For example, a 40-year-old woman with a blood pressure of 160/95 but no other cardiovascular risk factors has less than a 5% chance of a cardiovascular event within 10 years; if she is diabetic with evidence of left ventricular hypertrophy, her chance increases to 33%. In comparison, a 60-year-old woman with a blood pressure of 160/90 has a baseline 20% risk of a cardiovascular event within 10 years; with diabetes, her risk approaches 40%.[73] The new Joint National Committee VI hypertension guidelines advocate a risk stratification with lifestyle modification for up to a year in those with mild hypertension ($<160/<100$) and no risk factors or end-organ disease.[5]

Our study has several limitations. First, there were too few events in women for several outcomes, limiting our ability to detect a significant effect. This was most problematic for coronary outcomes and all outcomes in younger white women. Also, evidence of end-organ damage, such as left ventricular hypertrophy, was not included as a study outcome. These subclinical events may be more likely in younger hypertensive women than severe cardiovascular events in the first 5 years of treatment. Thus, a greater treatment benefit may have been noted in younger women if subclinical events were included as outcomes. We were not able to evaluate the long-term benefit or harm of treating younger women since the follow-up period for most studies ranged from 2.2 to 5 years. The only study with a 12-year follow-up period was in an elderly population.[24] It is possible that treatment of hypertension in young women would result in decreased risk of cardiovascular events over a longer period of time. Of note, however, hypertension trials in the elderly clearly demonstrate that a signficant risk reduction is attainable within a few years with initiation of treatment at older ages. The Australian study[21] and European Working Party on High Blood Pressure in the Elderly trial[27] both stopped following patients after a nonfatal event, which may result in an underestimation for mortality outcomes. However, the underestimation should equally affect both control and treated populations and, consequently, should influence only the confidence intervals surrounding the summary estimates, not the summary estimates themselves. We were not able to obtain results according to gender from one eligible study, the Treatment of Mild Hypertension Study.[54] However, this trial included only 345 women, who had low event rates and would not likely influence our results. As mentioned, our pooled data for African-American women came from only three studies,[14,16,23] as did the data for women aged 30 to 54 years,[13,14,21] with the majority of data for African-American women from the HDFP study (85%), and the majority of data for younger women from the MRC study (75%). Therefore, our results for African-American and younger women are most generalizable to hypertensive women who are similar to the study populations enrolled in the HDFP study and MRC study, respectively.

Clearly, many other questions remain outside the scope of the present data on women and hypertension. We hope future studies will enroll greater numbers of younger and nonwhite patients in order to further clarify not only the effect of hypertension treatment, but also the most effective medication choices for different subgroups, the optimal age to start or stop treatment, treatment effects in patients with specific comorbidities, and patient utility and compliance with treatment options.

In conclusion, hypertension treatment greatly decreases the relative and absolute risk of cerebrovascular and cardiovascular outcomes in women aged 55 years and older and in both younger and older African-American women. African-American women treated for hypertension also have significant risk reduction in coronary and all-cause mortality outcomes. A greater effort should be made to treat hypertension in these groups of women. In contrast, treatment of hypertension in white women aged 30 to 54 years did not show statistically significant benefit or harm. Decisions for treatment of hypertension in younger white women should be influenced by the individual patient's absolute risk of cardiovascular disease.

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