Reporting on sex-based analysis in clinical trials of angiotensin-converting enzyme inhibitor and angiotensin receptor blocker efficacy

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BACKGROUND: Clinical practice recommendations for hypertension do not make recommendations specific to men or women. However, the sex hormones appear to modulate differently the renin-angiotensin system (RAS), which plays a central role in the regulation of blood pressure. Today, little is known about the effects of sex on the efficacy of therapies that antagonize the RAS, such as angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs).

OBJECTIVE: To identify randomized controlled trials evaluating the efficacy of ACEIs and ARBs in preventing major cardiovascular outcomes, determine what proportion of the trial participants were female, and evaluate whether there was any evidence of a sex difference in the efficacy of these agents.

METHODS: A systematic review of the literature was conducted to identify randomized controlled trials that used either ACEIs or ARBs for the treatment of hypertension.

RESULTS: Thirteen ACEI trials and nine ARB trials were identified. Sex-specific outcome data were available in six of the ACEI trials and three of the ARB trials. These trials enrolled 74,105 patients; 39.1% were women. Seven of the nine trials indicated that ACEIs or ARBs may be slightly more beneficial in men. The magnitude of these differences, in most trials, was small.

CONCLUSIONS: Sex-specific data are reported in 43% of large hypertension clinical trials. Review of the trials reporting sex-specific effect sizes indicates that ACEIs and ARBs may be more effective in men.

Key Words: ACE inhibitors; Angiotensin receptor blockers; Efficacy; Hypertension; Sex

Compte rendu d'une analyse selon le sexe d'essais cliniques sur l'efficacité de l'inhibiteur de l'enzyme de conversion de l'angiotensine et des antagonistes de l'angiotensine

HISTORIQUE : Les recommandations de pratique clinique au sujet de l'hypertension ne sont pas axées sur les hommes ou les femmes. Cependant, les hormones sexuelles semblent moduler différemment le système rénine-angiotensine (SRA) qui joue un rôle essentiel dans la régulation de la tension artérielle. On ne sait pas grand-chose au sujet des effets du sexe sur les thérapies qui antagonisent le SRA, telles que les inhibiteurs de l'enzyme de conversion de l'angiotensine (IECA) et les antagonistes de l'angiotensine (AGA).

OBJECTIF : Repérer les essais aléatoires et contrôlés évaluant l'efficacité des IECA et de l'AGA pour prévenir les graves issues cardiovasculaires, déterminer la proportion des participants aux essais qui étaient de sexe féminin et évaluer s'il y avait une différence selon le sexe dans l'efficacité de ces agents.

MÉTHODOLOGIE : Les auteurs ont procédé à une analyse bibliographique systématique pour repérer les essais aléatoires et contrôlés qui faisaient appel soit aux IECA, soit aux AGA pour traiter l'hypertension.

RÉSULTATS : Les auteurs ont répertorié 13 essais sur les IECA et neuf sur les AGA. Ils ont obtenu des données d'issues selon le sexe dans six des essais sur les IECA et trois de ceux sur les AGA. Ces essais portaient sur 74 105 patients, dont 39,1 % étaient des femmes. Sept des neuf essais indiquaient que les IECA ou les AGA pourraient être légèrement plus efficaces chez les hommes. Dans la plupart des essais, la magnitude de ces différences était minime.

CONCLUSIONS : Les données selon le sexe sont déclarées dans 43 % des grands essais cliniques sur l'hypertension. D'après l'analyse des essais faisant état de l'importance des effets selon le sexe, les IECA et les AGA seraient plus efficaces chez les hommes.

Cardiovascular disease (CVD) is the leading cause of death among Canadian women. Hypertension is an established and prevalent risk factor for CVD, affecting more than one in five Canadian adults (1,2). In the Effect of Potentially Modifiable Risk Factors Associated with Myocardial Infarction in 52 Countries (INTERHEART) study (3), hypertension contributed to 29% of the population attributable risk for acute myocardial infarction in women compared with 15.9% with men, in part because the women were approximately one decade older. The prevalence of hypertension differs among men and women, as does the risk of CVD. Men develop clinically significant hypertension earlier, and among men 18 to 34 years of age, one in 10 are hypertensive compared with 2% of women; however, beyond 65 years of

age, over 50% are hypertensive, and the prevalence of hypertension in women remains greater than in men (4).

In addition to sex differences in epidemiology, there is evidence that there may be sex differences in the pathophysiology of hypertension. The renin-angiotensin system (RAS) plays a significant, if not central, role in the regulation of blood pressure (5,6). Endogenous sex hormones have been shown to interact with the RAS (Table 1). Androgens have been shown to upregulate the RAS and appear to produce an overall vasopressor effect (7). Estrogens, however, are in some way protective, with indirect evidence from an inverse relationship between the age of menopause and blood pressure (8). Also, the RAS is overall antagonized by estrogens (9).

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TABLE 1
Summary of the effects of sex steroid hormones on the renin-angiotensin system

Testosterone
Increased angiotensinogen messenger RNA
Increased plasma renin activity
Estrogen
Increased angiotensinogen
Decreased plasma renin activity
Decreased angiotensin-converting enzyme expression
Decreased angiotensin 1 receptor expression

In recent years, there has been a great deal of interest in the determinants of CVD in women (10). Historically, women have been under-represented in clinical trials that examine the efficacy of cardioprotective medications (11,12). As a result, the treatment effects noted in women in these trials are less precise than those for men, and these trials are underpowered to explicitly examine sex differences in drug efficacy. Recognizing the importance of having evidence-based treatment for both men and women, national granting agencies in the United States and Canada have implemented regulations on the enrolment of both sexes into clinical treatment trials and the reporting of sex-specific outcomes (13,14).

Presently, drugs that target the RAS (particularly angiotensin-converting enzyme inhibitors [ACEIs] and angiotensin receptor blockers [ARBs]) are the most commonly prescribed antihypertensive agents for both men and women (15). The objective of the present review was to provide a 'needs assessment' for clinical research in hypertension in women, with a specific focus on therapeutic efficacy of ACEIs and ARBs. To that end, we reviewed data from randomized clinical trials of hypertension that examined the efficacy of drugs that inhibit the RAS (specifically ACEIs and ARBs) to determine what proportion of study participants were female, how frequently sex-specific results were reported and to assess for any evidence of sex differences in treatment efficacy.

LITERATURE REVIEW

Medline, Embase, Cochrane Register of Clinical Trials and previous meta-analyses (16,17) were searched to identify trials that examined the efficacy of ACEIs or ARBs in preventing CV end points when used in the management of hypertension. Studies were included if they compared an ACEI or ARB with placebo or an active control, examined the composite end point of 'any major cardiovascular events' (consisting of myocardial infarction, stroke or death) as a primary or secondary end point, and reported effect sizes for men and women. To ensure capture of all potentially relevant trials, we did not exclude trials that enrolled subjects with established vascular disease, diabetes or nephropathy. Trials that enrolled participants acutely after myocardial infarction, and those with left ventricular dysfunction or congestive heart failure, as well as non-English publications, were excluded.

ACEI trials

Our review of the literature identified 13 large clinical trials in which the efficacy of ACEIs in preventing CV events has been evaluated (18-30). These trials enrolled a total of 82,227 participants, 35.7% of whom were women. Six of these trials examined the efficacy of ACEIs in the primary prevention of CV events (Second Australian National Blood Pressure study [ANBP-2] [27], Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial [ALLHAT] [21] and Second Swedish Trial in Old Patients with Hypertension [STOP-2] [24], which enrolled hypertensive participants, and Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial [FACET] [26], United Kingdom Prospective Diabetes Study [UKPDS 39] [19] and

Appropriate Blood Pressure Control in Diabetes [ABCD] [25], which enrolled hypertensive subjects with diabetes). Four trials enrolled subjects with known but stable CVD and examined the efficacy of ACEIs in secondary prevention (Heart Outcomes Prevention Evaluation [HOPE] [30], European trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease [EUROPA] [23], Japan Multicenter Investigation for Cardiovascular Diseases-B [JMIC-B] [29] and Perindopril Protection Against Recurrent Stroke Study [PROGRESS] [20]). One trial (Captopril Prevention Project [CAPPP] [18]) examined both primary and secondary prevention efficacy in a hypertensive population. Two trials (Diabetics Exposed to Telmisartan and Enalapril [DETAIL] [22] and African American Study of Kidney Disease [AASK] [28]) enrolled patients with known renal disease and examined the efficacy of preventing vascular events as a secondary end point.

Among these trials, sex-specific effect sizes were reported in only six studies (ANBP-2, ALLHAT, HOPE, EUROPA, FACET and JMIC-B) (Table 2). Sex-adjusted analyses were conducted in three (AASK, CAPPP and STOP-2) of the 13 identified studies, and the remaining studies did not report on sex-specific effect sizes or perform sex-adjusted analyses (Table 3).

Summary of results from trials reporting sex-specific outcomes:

Overall, 26,807 women were included in these trials. They represented 36% of all participants. Sex-specific patient characteristics were not reported in any of the trials.

Of the trials that did report sex-specific effect sizes, two trials examined the efficacy of ACEIs in the primary prevention of CVD in a population of older adults with hypertension. ANBP-2 randomly assigned 6083 adults (65 to 84 years of age) to enalapril or a thiazide diuretic (27) with a target blood pressure of lower than 160/90 mmHg. The primary end point was any major CV event (MACE) that included myocardial infarction, stroke or death by any cause. The event rate was significantly higher among men (907 events among 2981 men) compared with women (524 events among 3102 women). Men receiving enalapril had significantly fewer events than those on diuretic (RR=0.83; P=0.02). However, women on enalapril had virtually the same number of events irrespective of treatment with enalapril or diuretic (RR=1.0; P=0.98). A sex-treatment interaction was explicitly tested, but was not found to be statistically significant.

Similarly, ALLHAT (21) examined the efficacy of ACEIs in the primary prevention of CVD in adults 55 years of age or older with stage 1 or 2 hypertension. However, this trial differed from ANBP-2 with respect to its size and scope. ALLHAT was a multinational study that enrolled 33,357 participants. Of these participants, 24,309 were randomly assigned in a fixed allocation to chlorthalidone (n=15,255) or lisinopril (n=9054). Fifty-three per cent of the trial participants were female. In the subgroup analyses examining sex differences, the ALLHAT Investigators did not find a significant sex difference in treatment effect, but noted a trend toward improved outcome with ACEIs among men compared with women (men RR=0.94 [95% CI 0.85 to 1.05], women RR=1.06 [95% CI 0.92 to 1.23]).

FACET (26) was another CV primary prevention study; however, FACET differed from ALLHAT and ANBP-2 in that its study population included hypertensive adults with diabetes. This small trial enrolled 380 adults with type 2 diabetes (mean age 63 years). One hundred fifty-five women were enrolled. Sex differences were analyzed in a prespecified subgroup analysis, and a treatment-sex interaction was explicitly examined. The effect size noted in men and women was quite similar; both sexes appeared to benefit from treatment with fosinopril, relative to amlodipine, in preventing the primary end point of MACE (men hazard ratio = 0.53 [95% CI 0.17 to 1.62], women hazard ratio = 0.55 [95% CI 0.25 to 1.22]). It should be noted that the due to the small sample size, the CI surrounding these sex-specific effect sizes were very wide.

Three of the identified trials examined the efficacy of ACEIs in the secondary prevention of CV events (23,29,30). HOPE (30), EUROPA (23) and JMIC-B (29) all enrolled patients with stable

TABLE 2
Summary of trials reporting sex-specific outcomes

Trial	Agent	Comparator	Men, n Women, n	Outcome	Study population	Effect (men)* Effect (women)*
Angiotensin receptor blockers						
VALUE (n=15,245)	Valsartan	Amlodipine	8777 6468	CV morbidity and mortality	Adults at high risk of hypertension	0.94 (0.83–1.07) 1.21 (1.03–1.42)
SCOPE (n=4923)	Candesartan	Thiazide	1757 3166	Major CV event†	Adults 70–89 years old with hypertension	0.86 (0.67–1.12) 0.92 (0.72–1.17)
Angiotensin-converting enzyme inhibitors						
ANBP-2 (n=6083)	Enalapril	Thiazide	2981 3102	Major CV event	Adults 65–84 years old with hypertension	0.83 (0.71–0.97) 1.00 (0.83–1.21)
ALLHAT (n=24,309)	Lisinopril	Chlorthalidone	15,255 11,358	Major CV event	Adults >55 years old with hypertension	0.94 (0.85–1.05) 1.06 (0.92–1.23)
HOPE (n=9297)	Ramipril	Placebo	6819 2478	Major CV event	Adults with stable CAD or diabetes and one other vascular risk factor	0.76 (0.5–0.88) 0.79 (0.69–0.98)
EUROPA (n=12,218)	Perindopril	Placebo	10,439 1779	Myocardial infarction, CV mortality or CV arrest	Adults with stable CAD	0.8 (P<0.05) 0.79 (P<0.05)
JMIC-B (n=1650)	Imidapril	Nifedipine	1135 515	Cardiac events, including mortality	Hypertensive adults with stable CAD	0.96 (0.72–1.34) 1.28 (0.76–2.14)
FACET (n=380)	Fosinopril	Amlodipine	225 115	Major CV event	Adults with hypertension and diabetes	0.53 (0.17–1.62) 0.55 (0.25–1.22)

*With the exception of the Japan Multicenter Investigation for Cardiovascular Diseases-B (JMIB-B), effects are reported as RR where the event rate in the angiotensin receptor blocker or angiotensin-converting enzyme inhibitor is the numerator and the event rate in the control group is the denominator. In JMIB-B, the event rate in the imidapril group was the denominator and nifedipine event rate was the numerator; †Major cardiovascular (CV) events include myocardial infarction, stroke and death. ALLHAT Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ANBP-2 Second Australian National Blood Pressure study; CAD Coronary artery disease; EUROPA European trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease; FACET Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial; HOPE Heart Outcomes Prevention Evaluation; SCOPE Study on COgnition and Prognosis in the Elderly; VALUE Valsartan Antihypertensive Long-term Use Evaluation

coronary artery disease or coronary disease equivalents (HOPE included patients with diabetes and one other CV risk factor). HOPE and EUROPA were of similar size, with approximately 10,000 participants, and JMIB-B was smaller, enrolling 1650 participants. Men significantly outnumbered women in each of these trials; HOPE and EUROPA had a male to female ratio of 3:1 and JMIB-B had a ratio of 2:1. In HOPE, men treated with an ACEI were noted to have a 24% relative reduction (95% CI 12% to 35%) in all major CV events compared with a 21% relative reduction (95% CI 10% to 31%) in women who were treated with an ACEI. This difference was not significant. In EUROPA, the results were virtually identical, in that both men and women appeared to benefit from treatment with an ACEI (men RR=0.80, women RR=0.79). These estimates of effect were not found to be significantly different.

JMIB-B, although a secondary prevention trial, differed from HOPE and EUROPA in that it was not a placebo-controlled trial; rather, the comparator agent in this study was nifedipine. This trial had slightly different results, but also had a slightly lower composite event rate. This trial did not find any statistically significant sex differences in efficacy in their subgroup analysis, but noted that men on nifedipine had a 4% (men RR=0.96 [95% CI 0.72 to 1.34]) lower RR of CV events compared with men on imidapril, while women on imidapril had a 28% lower risk of a CV event relative to women on nifedipine (women RR=1.28 [95% CI 0.76 to 2.14]).

ARB trials

Our review of the literature revealed nine large randomized control trials that examined the efficacy of ARBs in preventing vascular events among those with hypertension (Diabetics Exposed to Telmisartan and Enalapril [DETAIL] [22], Losartan Intervention for Endpoint reduction in hypertension [LIFE] [31], Irbesartan in Diabetic Nephropathy Trial [IDNT] [32], Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan [RENAAL] [33], Acute

Candesartan Cilexetil therapy in Stroke Survivors [ACCESS] [34], MOrbidity and mortality after Stroke, Eprosartan compared with nitrendipine in Secondary prevention [MOSES] [35], Efficacy of Candesartan on Outcome in Saitama Trial [E-COST] [36], Study on COgnition and Prognosis in the Elderly [SCOPE] [37] and Valsartan Antihypertensive Long-term Use Evaluation [VALUE] [38]). These trials enrolled 34,811 patients, with 48.5% female participation. The ARB trials and ACEI trials were similar with respect to the patient populations of interest. However, for secondary prevention trials, while ACEI trials tended to enrol participants with stable coronary artery disease, ARB trials enrolled subjects with established cerebrovascular disease or diabetic kidney disease. Three trials examined the efficacy of ARBs in the primary prevention of vascular events in high-risk hypertensive patients (LIFE, SCOPE and VALUE) (Table 2) (31,37,38). Two of the identified trials examined the efficacy of ARBs in preventing recurrent CV events and related morbidities following stroke (ACCESS [34] and MOSES [35]). Three other trials examined the efficacy of ARBs in preventing progression of diabetic nephropathy, with prevention of vascular events examined as a prespecified secondary end point (DETAIL [22], IDNT [32] and RENAAL [33]). Of all the trials identified, only three (SCOPE [37], LIFE [31] and VALUE [38]) reported outcomes in men and women. The remaining six trials did not report sex-specific outcomes nor did they perform sex-adjusted analyses (22,32–36).

Summary of results from trials reporting sex-specific outcomes: Overall, 14,276 women were included in these trials. They represented 49.7% of all participants.

All of the trials reporting sex-specific outcome data were primary prevention trials. VALUE also enrolled participants with known and stable CVD and therefore also examined efficacy in secondary prevention. All three trials enrolled individuals at high risk of a vascular event due to the presence of left ventricular hypertrophy (LIFE), other CV risk factors, stable CVD or CVD equivalents (VALUE) or

TABLE 3
Summary of trials not reporting sex-specific outcomes

Study	Agent	Comparator	Population	Men, n (%)	Women, n (%)	Primary end point	RR (95% CI)	Sex-adjusted analysis
Angiotensin-converting enzyme inhibitors								
UKPDS 39	Captopril	Atenolol	HTN and DM2	410 (54)	348 (46)	Composite diabetes end point*	1.10 (0.86–1.41)	No
ABCD	Enalapril	Nisoldipine	HTN and DM2	317 (67)	153 (33)	24 h creatinine clearance	Not applicable	No
CAPPP	Captopril	Atenolol or metoprolol	HTN	5874 (53)	5111 (47)	Major CV event†	1.05 (P=0.52)	Yes
STOP-2	Enalapril or lisinopril	Diuretic or beta-blocker	HTN and elderly	2183 (33)	4431 (67)	CV mortality	1.0 (0.84–1.22)	Yes
PROGRESS	Perindopril	Indapamide	Post-CVA	4253 (70)	1852 (30)	Fatal/nonfatal CVA	0.72 (0.62–0.83)	No
AASK	Ramapril	Metoprolol or amlodipine	African-American, HTN and renal insufficiency	670 (61)	424 (39)	Composite renal end point‡	0.78 (0.62–0.99)† 0.62 (0.44–0.86)§	Yes
Angiotensin receptor blockers								
E-COST	Candesartan	CCB-based therapy	HTN	983 (48)	1065 (52)	Myocardial infarction, CVA or CHF	0.61 (0.41–0.84)	No
ACCESS	Candesartan	Placebo	HTN post-CVA	173 (52)	166 (48)	Case fatality and disability	0.48 (0.25–0.90)	No
MOSES	Eprosartan	Nitrendapine	HTN post-CVA	733 (54)	619 (46)	Major CV event	0.79 (0.66–0.96)	No
IDNT	Irbesartan	Amlodipine or placebo	HTN, DM2 and proteinuria	1140 (66)	575 (34)	Composite renal end point¶	0.77 (P=0.006)	No
RENAAL	Irbesartan	Placebo	HTN, DM2 and proteinuria	267 (67)	129 (23)	Time to overt nephropathy	0.56 (0.31–0.99)	No
DETAIL	Telmisartan	Enalapril	HTN, DM2	182 (73)	68 (27)	Rate of change in GFR	Not applicable	No

*Any diabetes-related end point includes any fatal or nonfatal diabetes-related vascular event, diabetes-related death and all-cause mortality; †Major cardiovascular (CV) events include myocardial infarction, stroke and death; ‡Ramapril versus metoprolol; §Ramapril versus amlodipine; ¶Composite renal end point includes doubling of serum creatinine, need for dialysis, transplant or death. AASK African American Study of Kidney Disease; ABCD Appropriate Blood Pressure Control in Diabetes; ACCESS Acute Candesartan Cilexetil therapy in Stroke Survivors CAPPP Captopril Prevention Project; CCB Calcium channel blocker; CHF Congestive heart failure; CVA Cerebrovascular accident; DETAIL Diabetics Exposed to Telmisartan and Enalapril; DM2 Diabetes mellitus type 2; E-COST Efficacy of Candesartan on Outcome in Saitama Trial; GFR Glomerular filtration rate; HTN Hypertension; IDNT Irbesartan in Diabetic Nephropathy Trial; MOSES Morbidity and mortality after Stroke, Eprosartan compared with nitrendipine in Secondary prevention; PROGRESS Perindopril Protection Against Recurrent Stroke Study; RENAAL Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan; STOP-2 Second Swedish Trial in Old Patients with Hypertension; UKPDS 39 United Kingdom Prospective Diabetes Study

advanced age (SCOPE). LIFE and SCOPE examined the efficacy of candesartan in preventing the primary composite end point of any MACE. VALUE differed slightly in that it examined the efficacy of valsartan in the primary and secondary prevention of CV events or CV-related morbidity. Women were well represented in these three trials and accounted for approximately 50% of the over 30,000 participants enrolled. SCOPE did not find a statistically significant difference in the efficacy of candesartan in preventing major CV events, although men appeared to benefit slightly more than women. Women receiving ARBs, however, appeared to benefit more in terms of stroke prevention compared with men. VALUE, however, found the opposite. In a subgroup analysis, men were found to have a lower CV event rate on the ARB valsartan, but women had a lower event rate on the active comparator amlodipine. While the LIFE trial (39) examined MACE as its primary end point, the authors reported sex-specific effect sizes only on the outcome of “regression of left ventricular hypertrophy”, as measured by voltage changes on electrocardiogram. This analysis revealed that both men and women had greater reduction in electrocardiogram voltage when treated with ARBs; however, the magnitude of this reduction was greater in men, suggesting that men may have greater regression of left ventricular hypertrophy on ARBs than women. However, a statistically significant sex-treatment interaction was not found.

DISCUSSION

The present literature review identified 21 large randomized controlled trials that examined the efficacy of ACEIs and ARBs in

preventing CV events. Among the ACEI trials, women accounted for 37.5% of trial participants. Women were better represented among the ARB trials, among which they comprised 48.5% of the participants. Of these trials, only nine reported sex-specific effect sizes. While one trial (ANBP-2) did find a significant sex difference in treatment effect, the majority of trials did not have adequate power to evaluate such sex differences. The examinations for sex differences were performed as subgroup analyses and should be interpreted with caution. However, it is interesting that with the exception of the two smallest trials (JMIC-B and FACET), the ACEI trials demonstrated a consistent trend of greater benefit of these agents in men.

It should be noted that with the exception of the difference noted in the ANBP-2 study, in which women were found to have no benefit from ACEIs, the magnitudes of these different effect sizes among men and women are small, and may not be clinically significant. Furthermore, women accounted for approximately 25% of participants in HOPE, EUROPA and JMIC-B, so the effect size demonstrated in women is much less precise than that reported in men. Nonetheless, the present review raises the question of whether ACEIs are equally efficacious in men and women. While the review focused on the management of hypertension, previous population-based studies examining potential sex differences in ACEI efficacy in the treatment of congestive heart failure, it also found that men on ACEIs receive more benefit with respect to mortality reduction than women on ACEIs (40,41).

A similar pattern of study outcomes was noted among the ARB trials. Three of nine identified trials examined the efficacy of ARBs in

preventing CV events reported sex-specific effect sizes. All of these trials found that the men appeared to benefit more from ARBs on the end points of MACE, CV mortality and morbidity, and regression of left ventricular hypertrophy. While VALUE found a significant sex difference, the benefits noted in LIFE and SCOPE were smaller and of less clinical significance. The same caveats regarding subgroup analyses need to be applied to these findings. Subgroup analyses are hypothesis-generating endeavours, and due to small numbers, these analyses tend to be underpowered and imprecise.

What is most notable in the present review is that there were 12 trials that did not report sex-specific outcomes. Among these, only three trials tried to account for potential sex-differences by conducting sex-adjusted analyses. Women were well represented in these trials, accounting for 43% of the trial participants (women $n=2622$, total $n=6100$). It is of note that there was little evidence of benefit of the anti-RAS agents when sex-adjusted analyses were conducted. Given that there was a general trend toward benefit in nonadjusted analyses and that men were more numerous in these trials (particularly PROGRESS), it suggests that there may be some differential effects of these agents among men and women. The trials reporting sex-specific outcomes were larger and, collectively, provided data on a very large number of women. However, it is disappointing that in the ACEI studies, women still accounted for only one-third of the participants. In the ARB trials, women were much better represented; however, this likely reflects the fact that many trials recruited patients following stroke. While both coronary artery disease and stroke remain more common among younger men – among older age groups – the sex difference in prevalence attenuates. Thus, because ARB investigators selected older populations following stroke, the likelihood of enrolling more women was greater.

Limitations

The present review has limitations. It is a systematic narrative summary and does not provide a statistical summary of the evidence on ACEIs and ARBs in men compared with women. It should be noted that while sex-specific estimates of effect were reported in 41% of the identified trials, sex-specific event rates were rarely reported, which are necessary for conducting a statistical meta-analysis. Another limitation is that women of reproductive age were not well represented in these studies. While the mean age of female participants was not reported, the mean age of all the trial participants was 67.1 years. Therefore, these trials are examining ACEI and ARB efficacy among men and largely postmenopausal women. Given the potential influence of endogenous sex hormones on the RAS, it is reasonable to speculate that anti-RAS therapies may affect women differently depending on their reproductive status. There is limited evidence suggesting that among younger subjects, women may be more

responsive to anti-RAS therapy than men. Miller et al (42) found that women had more effective angiotensin receptor blockade in response to irbesartan administration than men in a population of healthy young participants (mean age of women 28 ± 2 years). Finally, the present review examined the efficacy of ACEIs and ARBs relative to placebo and active controls. The ability to appreciate a sex difference in the efficacy of ACEIs or ARBs is influenced by the comparator used in each trial, and it is possible that relative to men, women may benefit more from the comparator. We found a small signal that men may respond to ACEIs and ARBs better than women, but this effect was much smaller than the benefit women received from treatment of hypertension with these agents.

CONCLUSIONS

We have documented that women remain under-represented in trials of ACEIs: they only accounted for one-third of trial participants. There was good female representation in the ARB trials, in which women accounted for approximately one-half of enrolled participants. The ability to enrol a greater number of women in the ARB trials is likely due to the population of interest. We have also demonstrated that only 43% of trials reported sex-specific outcomes. Last, we have illustrated that there appears to be a trend toward anti-RAS therapy being slightly more efficacious in men.

There appears to be sexual dimorphism in the epidemiology and the pathophysiology of hypertension, and the present review suggests that this dimorphism may also extend to treatment efficacy for ACEIs and ARBs. However, there is still a lack of sufficient evidence to lead to sex-specific hypertension recommendations. Further evaluation of these differences is required to ensure the best possible care for both male and female patients living with hypertension. The present review also provides some encouragement, in that enrolling women is possible when the study population is carefully considered.

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REFERENCES

1. Joffres MR, Hamet P, MacLean DR, L'italien GJ, Fodor G. Distribution of blood pressure and hypertension in Canada and the United States. *Am J Hypertens* 2001;14:1099-105.
2. Wolf-Maier K, Cooper RS, Banegas JR, et al. Hypertension prevalence and blood pressure levels in 6 European countries, Canada, and the United States. *JAMA* 2003;289:2363-9.
3. Yusuf S, Hawken S, Ounpuu S, et al; INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): Case-control study. *Lancet* 2004;364:937-52.
4. Joffres MR, Ghadirian P, Fodor JG, Petrasovits A, Chockalingam A, Hamet P. Awareness, treatment, and control of hypertension in Canada. *Am J Hypertens* 1997;10:1097-102.
5. Gradman AH, Kad R. Renin inhibition in hypertension. *J Am Coll Cardiol* 2008;51:519-28.
6. Hammoud RA, Vaccari CS, Nagamia SH, Khan BV. Regulation of the renin-angiotensin system in coronary atherosclerosis: A review of the literature. *Vasc Health Risk Manag* 2007;3:937-45.
7. Reckelhoff JF. Gender differences in the regulation of blood pressure. *Hypertension* 2001;37:1199-208.
8. Izumi Y, Matsumoto K, Ozawa Y, et al. Effect of age at menopause on blood pressure in postmenopausal women. *Am J Hypertens* 2007;20:1045-50.
9. McGuire BB, Watson RW, Pérez-Barriocanal F, Fitzpatrick JM, Docherty NG. Gender differences in the renin-angiotensin and nitric oxide systems: Relevance in the normal and diseased kidney. *Kidney Blood Press Res* 2007;30:67-80.
10. Pilote L, Dasgupta K, Guru V, et al. A comprehensive view of sex-specific issues related to cardiovascular disease. *CMAJ* 2007;176:S1-44. (Erratum in 2007;176:1310).
11. Franklin SS. Definition and epidemiology of hypertensive cardiovascular disease in women: The size of the problem. *J Hypertens Suppl* 2002;20:S3-S5.
12. Geller SE, Adams MG, Carnes M. Adherence to federal guidelines for reporting of sex and race/ethnicity in clinical trials. *J Womens Health (Larchmt)* 2006;15:1123-31.

13. Pinn VW. The role of the NIH's Office of Research on Women's Health. *Acad Med* 1994;69:698-702.
14. Rochon PA, Clark JP, Binns MA, Patel V, Gurwitz JH. Reporting of gender-related information in clinical trials of drug therapy for myocardial infarction. *CMAJ* 1998;159:321-7. (Erratum in 1998;159:650).
15. Campbell NR, Tu K, Brant R, Duong-Hua M, McAlister FA; Canadian Hypertension Education Program Outcomes Research Task Force. The impact of the Canadian Hypertension Education Program on antihypertensive prescribing trends. *Hypertension* 2006;47:22-8.
16. Psaty BM, Lumley T, Furberg CD, et al. Health outcomes associated with various antihypertensive therapies used as first-line agents: A network meta-analysis. *JAMA* 2003;289:2534-44.
17. Rodrigues EJ, Eisenberg MJ, Pilote L. Effects of early and late administration of angiotensin-converting enzyme inhibitors on mortality after myocardial infarction. *Am J Med* 2003;115:473-9.
18. The Captopril Prevention Project: A prospective intervention trial of angiotensin converting enzyme inhibition in the treatment of hypertension. The CAPPP Group. *J Hypertens* 1990;8:985-90.
19. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. UK Prospective Diabetes Study Group. *BMJ* 1998;317:713-20.
20. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. *Lancet* 2001;358:1033-41. (Errata in 2001;358:1556, 2002;359:2120).
21. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002;288:2981-97. (Errata in 2003;289:178, 2004;291:2196).
22. Barnett AH, Bain SC, Bouter P, et al; Diabetics Exposed to Telmisartan and Enalapril Study Group. Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. *N Engl J Med* 2004;351:1952-61. (Erratum in 2005;352:1731).
23. Fox KM; EUROpean trial On reduction of cardiac events with perindopril in stable coronary Artery disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: Randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet* 2003;362:782-8.
24. Hansson L, Lindholm LH, Ekblom T, et al. Randomised trial of old and new antihypertensive drugs in elderly patients: Cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study. *Lancet* 1999;354:1751-6.
25. Schrier RW, Estacio RO. Additional follow-up from the ABCD trial in patients with type 2 diabetes and hypertension. *N Engl J Med* 2000;343:1969.
26. Tatti P, Pahor M, Byington RP, et al. Outcome results of the Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (FACET) in patients with hypertension and NIDDM. *Diabetes Care* 1998;21:597-603.
27. Wing LM, Reid CM, Ryan P, et al; Second Australian National Blood Pressure Study Group. A comparison of outcomes with angiotensin-converting – enzyme inhibitors and diuretics for hypertension in the elderly. *N Engl J Med* 2003;348:583-92.
28. Wright JT Jr, Bakris G, Greene T, et al; African American Study of Kidney Disease and Hypertension Study Group. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: Results from the AASK trial. *JAMA* 2002;288:2421-31. (Erratum in 2006;295:2726).
29. Yui Y, Sumiyoshi T, Kodama K, et al; Japan Multicenter Investigation for Cardiovascular Diseases-B Study Group. Comparison of nifedipine retard with angiotensin converting enzyme inhibitors in Japanese hypertensive patients with coronary artery disease: The Japan Multicenter Investigation for Cardiovascular Diseases-B (JMIB-B) randomized trial. *Hypertens Res* 2004;27:181-91.
30. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000;342:145-53. (Errata in 2000;342:1376, 2000;342:748).
31. Kizer JR, Dahlöf B, Kjeldsen SE, et al. Stroke reduction in hypertensive adults with cardiac hypertrophy randomized to losartan versus atenolol: The Losartan Intervention For Endpoint reduction in hypertension study. *Hypertension* 2005;45:46-52.
32. Lewis EJ, Hunsicker LG, Clarke WR, et al; Collaborative Study Group. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001;345:851-60.
33. Parving HH, Lehnert H, Bröchner-Mortensen J, Gomis R, Andersen S, Arner P; Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study Group. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med* 2001;345:870-8.
34. Schrader J, Lüders S, Kulschewski A, et al; Acute Candesartan Cilexetil Therapy in Stroke Survivors Study Group. The ACCESS Study: Evaluation of Acute Candesartan Cilexetil Therapy in Stroke Survivors. *Stroke* 2003;34:1699-703.
35. Schrader J, Lüders S, Kulschewski A, et al; MOSES Study Group. Morbidity and Mortality After Stroke, Eprosartan Compared with Nitrendipine for Secondary Prevention: Principal results of a prospective randomized controlled study (MOSES). *Stroke* 2005;36:1218-26.
36. Suzuki H, Kanno Y; Efficacy of Candesartan on Outcome in Saitama Trial (E-COST) Group. Effects of candesartan on cardiovascular outcomes in Japanese hypertensive patients. *Hypertens Res* 2005;28:307-14. (Erratum in 2005;28:553).
37. Trenkwalder P, Elmfeldt D, Hofman A, et al; The Study on COgnition and Prognosis in the Elderly (SCOPE). The Study on COgnition and Prognosis in the Elderly (SCOPE) – major CV events and stroke in subgroups of patients. *Blood Press* 2005;14:31-7.
38. Zanchetti A, Julius S, Kjeldsen S, et al. Outcomes in subgroups of hypertensive patients treated with regimens based on valsartan and amlodipine: An analysis of findings from the VALUE trial. *J Hypertens* 2006;24:2163-8.
39. Okin PM, Devereux RB, Jern S, et al; Losartan Intervention for Endpoint reduction in hypertension Study Investigators. Regression of electrocardiographic left ventricular hypertrophy by losartan versus atenolol: The Losartan Intervention for Endpoint reduction in Hypertension (LIFE) Study. *Circulation* 2003;108:684-90.
40. Hudson M, Rahme E, Behloul H, Sheppard R, Pilote L. Sex differences in the effectiveness of angiotensin receptor blockers and angiotensin converting enzyme inhibitors in patients with congestive heart failure – a population study. *Eur J Heart Fail* 2007;9:602-9.
41. Keyhan G, Chen SF, Pilote L. Angiotensin-converting enzyme inhibitors and survival in women and men with heart failure. *Eur J Heart Fail* 2007;9:594-601.
42. Miller JA, Cherney DZ, Duncan JA, et al. Gender differences in the renal response to renin-angiotensin system blockade. *J Am Soc Nephrol* 2006;17:2554-60.