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Gender Differences in Cardiovascular Outcomes in Patients with Incident Hypertension

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Abstract

Background—The time of initial hypertension diagnosis represents an opportunity to assess subsequent risk of adverse cardiovascular outcomes. The extent to which women and men with newly identified hypertension are at similar risk for adverse cardiovascular events, including chronic kidney disease, is not well known.

Methods—Among women and men with incident hypertension from 2001–2006 enrolled in the Cardiovascular Research Network (CVRN) Hypertension Registry, we compared incident events including all-cause death; hospitalization for myocardial infarction (MI), heart failure (HF), or stroke; and the development of chronic kidney disease (CKD). Multivariable models adjusted for patient demographic and clinical characteristics.

Results—Among 177,521 patients with incident hypertension, 55% were women. Compared to men, women were older, more likely white and had more kidney disease at baseline. Over median 3.2 years (IQR 1.6–4.8) of follow-up, after adjustment, women were equally likely to be hospitalized for HF (HR 0.90, 95% CI 0.76–1.07) and were significantly less likely to die of any cause (HR 0.85, 95% CI 0.80–0.90) or be hospitalized for MI (HR 0.44, 95% CI 0.39–0.50) or stroke (HR 0.68, 95% CI 0.60–0.77) compared to men. Women were significantly more likely to develop chronic kidney disease (9.60% vs. 7.15%; adjusted HR 1.17, 95% CI 1.12–1.22) than men.

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DISCLOSURES

All authors report no conflicts of interest in regards to this manuscript.

Conclusion—In this cohort with incident hypertension, women were more likely to develop chronic kidney disease and less likely to develop other cardiovascular outcomes compared to men. Future studies should investigate the potential reasons for these gender differences.

BACKGROUND

Cardiovascular disease (CVD) is the leading cause of death and disability among men and women worldwide.[1, 2] Hypertension is a major risk factor for the development of CVD including stroke, congestive heart failure, myocardial infarction as well as renal failure and all-cause mortality.[3] Observational studies and randomized trials of have shown that hypertension treatment dramatically decreases CVD morbidity and mortality for both men and women.[4, 5]

The time of initial hypertension diagnosis represents an opportunity to identify and potentially modify subsequent cardiovascular risk. The extent to which women and men with newly identified hypertension are at a similar risk for subsequent CVD outcomes is debated. Some studies suggest women with hypertension have higher rates of subsequent stroke, while others suggests women are at lower risk of other CVD outcomes such as myocardial infarction. [6–8] Furthermore, controversy exists as to whether women and men with hypertension are at equal risk of developing chronic renal disease. [9–13] Prior work in this area is limited by the use of cross sectional designs, small historical cohorts, an inability to account for incident hypertension, a limited number of women, or an inability to longitudinally follow for multiple CVD outcomes.

The objective of this study is to compare the rates of incident CVD outcomes among men and women with incident hypertension in a contemporary, ambulatory cohort of patients followed in three large integrated health care systems for median 3.2 years (>550,000 person years). We compared the risk of subsequent death, and incident myocardial infarction, stroke, heart failure and chronic kidney disease between women and men.

METHODS

Study Population

The study sample included all patients within the Cardiovascular Research Network (CVRN) hypertension registry from 2001–2006 with incident hypertension. The development of the CVRN hypertension registry has been described previously.[14, 15] In brief, a retrospective cohort of patients with hypertension in three integrated health systems (HealthPartners of Minnesota, Kaiser Permanente Colorado, and Kaiser Permanente Northern California) were identified using a published algorithm based upon ICD-9 diagnosis codes, blood pressure (BP) measurements (from non-urgent outpatient visits), and pharmacy data.[16] For this study, incident hypertension was defined as: 1) 2 consecutive elevated BPs and a subsequent hypertension diagnosis or hypertension treatment; OR 3 consecutive elevated BPs regardless of subsequent diagnosis or treatment; AND 2) no prior diagnosis or treatment for hypertension in 12 months prior to meeting entry criteria. Elevated BP was defined according to JNC7 thresholds of systolic blood pressure (SBP) 140 mm Hg or diastolic blood pressure (DBP) 90 mm Hg with lower cut-offs of SBP 130 mm Hg or DBP 80 mm Hg for those with diabetes mellitus or chronic kidney disease. [17] Given recent studies questioning the use of lower blood pressure cut-offs to define hypertension in patients with diabetes or chronic kidney disease, we performed additional analysis using SBP 140 mm Hg or DBP 90 mm Hg for all patients. [18, 19]

Since the study inclusion criteria rely on diagnoses codes and pharmacy data, patients were required to have continuous health plan enrollment for 1 year prior to cohort entry.

Because the approach to hypertension management differs in pregnancy, women with identified pregnancy were also excluded. The study was approved by the institutional review board of both health plans.

Independent Variables

The primary predictor variable for all analyses was patient gender. Other covariates considered in the multivariable models included: age, race/ethnicity, BP level at cohort entry, year of cohort entry, study site and coexisting medical conditions. Coexisting conditions were determined based on ICD-9 diagnosis codes assigned at visits or entered on problem lists, prescribed medications, and laboratory data according to a pre-specified algorithm.[20]

Outcome Variables

In our primary outcomes analysis, we compared incident cardiovascular events including myocardial infarction (MI), stroke, heart failure (HF), chronic kidney disease (CKD) or all-cause death. For each individual outcome, patients with a history of that outcome (prevalent cases) were excluded from the analysis. For a given outcome, a history of any of the other events was included as a covariate. Death was ascertained from internal health system databases and state death records. Primary hospital discharge diagnoses were used to identify incident cases of MI (ICD-9 codes 410), HF (ICD-9 codes 428, 398.91, 402, 404), and stroke (ICD-9 codes 430, 438.9). Importantly, data on hospitalizations occurring outside of each health system were available through administrative claims data, which are considered highly accurate as they are used for reimbursement for out-of-system utilization. Both diagnoses and laboratory measures of renal function were used to identify incident cases of CKD. Patients with previously normal renal function were considered to have progressed to CKD if, following cohort entry, they had a new diagnosis of kidney disease (ICD-9 codes: 585.1–585.9) or two consecutive estimated glomerular filtration (eGFR) rates less than 60 ml/min/1.73 m² based on the MDRD equation.[21]

Statistical Analysis

Baseline characteristics were compared between men and women using the chi-square test for categorical variables, two sample t-test or Wilcoxon rank sum tests for continuous variables. Next, unadjusted rates of the cardiovascular outcomes among the two groups were compared using the Wald chi-square tests. Incidence rates per person years of follow-up were also determined.

Freedom from the occurrence of the individual outcomes of death, non-fatal MI, HF, stroke and CKD were compared between men and women using the Kaplan-Meier method. Patients with a prior history of the events of interest were removed from that particular analysis (n=179 for MI, n=287 for CHF, n=1943 for stroke, and n=9488 for CKD). Freedom from an event was measured from the time of incident hypertension identification and censored at the time of death or the event of interest. Differences in event rates were evaluated with log-rank tests. Next, multivariable Cox proportional hazards regression models were constructed, adjusting for year of cohort entry, study site, baseline blood pressure, baseline eGFR, frequency of eGFR measurements and patient characteristics (race, age, socioeconomic status, body mass index and history of diabetes mellitus, peripheral vascular disease, asthma, cancer, connective tissue disease, chronic obstructive pulmonary disease, dementia, depression, hyperlipidemia, liver disease, pulmonary disease, thyroid disease, and peptic ulcer disease). Socioeconomic status was estimated by geocoding patients' residence address to the 2000 US Census data at the block group level. Patients were categorized as low socioeconomic status if they lived in a census area where at least 20% of residents had household incomes below the federal poverty level or at least 25% of

residents had less than a high school education. For a given outcome, a history of any of the other events was also included as a covariate.

Given lower eGFR among women compared to men at baseline, a secondary, matched cohort analysis was performed. Men and women were matched according to baseline age (within 1- year) and baseline eGFR (within 5 ml/min/1.73 m²). Baseline eGFR was calculated using the creatinine measurement within 90 days before or after entry into the incident hypertension cohort. Follow-up eGFR was compared at yearly intervals using the mean of all eGFR values over the preceding year. Repeated measures modeling with PROC MIXED was used to compare mean eGFRs at each year between men and women controlling for patient characteristics.

All analyses were performed using the SAS statistical package version 9.2 (SAS Institute, Cary, NC).

RESULTS

Of the 288,916 patients initially identified with incident hypertension in the CVRN hypertension registry, 108,294 (37.5%) were excluded because they did not have a full-year of prior membership, 3,037 (1.1%) patients were excluded because of pregnancy and 64 patients were excluded due to missing data. The final study cohort included 177,521 patients; of whom 55% were women.

Compared with men, women in the cohort were older and more likely to be white. Women had higher rates of many co morbidities at baseline including chronic kidney disease, cancer, depression, connective tissue disease, thyroid disease and lung disease compared to men. Women had lower rates of baseline diabetes and coronary artery disease. (Table 1)

Over a median follow-up of 3.2 years (IQR 1.6–4.8 years), 7,669 deaths (13.24 per 1000 person years) occurred and a total of 1,883 non-fatal MI (3.25 per 1000 person years), 882 heart failure (1.53 per 1000 person years), and 1617 stroke (2.82 per 1000 person years) hospitalizations occurred. A total of 14,267 patients developed chronic kidney disease as defined by a new diagnosis for kidney disease or a decline in eGFR (25.86 per 1000 person years). (Table 2)

In the unadjusted analysis, women tended to be equally likely to die of any cause (4.39% vs. 4.24%, $p=0.07$) or be hospitalized for HF (0.49% vs. 0.50%, $p=0.09$) compared to men. Women were less likely to develop incident MI (0.71% vs. 1.49%, $p<0.01$) or stroke (0.84% vs. 1.02%, $p<0.01$) and were more likely to develop chronic kidney disease (9.60% vs. 7.15%, $p<0.01$) compared to men. (Table 2)

In the multivariable models, most of these relationship persisted. Women remained equally likely to be hospitalized for HF (HR 0.90, 95% CI 0.76–1.07); however, over the follow-up period women were significantly less likely to die from any cause (HR 0.85, 95% CI 0.80–0.90) than men. Women continued to be significantly less likely to suffer MI (HR 0.44, 95% CI 0.39–0.50) or stroke (HR 0.68, 95% CI 0.60–0.76) and remained significantly more likely to develop CKD (HR 1.17, 95% CI 1.12–1.22) compared with men. (Table 2) Additional analyses using a common blood pressure cut-off to define hypertension for all patients (140/90 mm Hg) revealed no significant changes in these relationships (data not shown).

In the secondary matched cohort analysis, 40,312 pairs of women and men (45% of study cohort) were matched based on age (± 1 year) and baseline eGFR (± 5 ml/min/1.73 m²). As expected, the mean age and baseline eGFRs in the matched cohort were similar for men

and women (age 56.3 $\pm$ 13.0 vs. 56.3 $\pm$ 13.0; eGFR 83.4 ml/min/1.73 m² $\pm$ 17.2 vs. 82.8 ml/min/1.73 m² $\pm$ 17.9). Over 7 years of follow-up, after adjustment for patient characteristics and repeated eGFR measures over time, mean eGFR remained significantly lower in women compared to men (follow-up year 7 eGFR 72.8 ml/min/1.73 m² $\pm$ 20.7 in women vs. eGFR 75.1 ml/min/1.73 m² $\pm$ 21.5 in men; $p < 0.02$). When comparing the rate of eGFR decline (slopes) in this matched cohort, eGFR declined at a faster rate in women than in men (women -1.61 , men -1.38 ; $p < 0.0001$). (Figure 1)

DISCUSSION

In this contemporary cohort of patients with incident hypertension, over 3.2 years of median follow-up (25th quartile 1.6, 75th quartile 4.8 years), women were significantly more likely to have a new diagnosis of kidney disease or decline in eGFR and significantly less likely to die or to develop most other cardiovascular outcomes compared with men. Specifically, women had a 17% higher chance of developing chronic kidney disease compared to men. Women had lower chances of all-cause death (15%), incident myocardial infarction (56%) and incident stroke (32%) hospitalizations and equal chance of incident heart failure admissions compared to men.

Many studies including Framingham have investigated long term cardiovascular outcomes among those with elevated blood pressure, however, few have compared these outcomes among a large cohort of women and men with incident hypertension.[8] The time of hypertension identification represents a unique opportunity to differentiate and potentially modify subsequent cardiovascular risk. Beyond including patients at the time of hypertension identification, additional strengths of this study include use of a large, contemporary clinical population followed in 3 large healthcare systems, the high percentage of women in the study cohort and ability to longitudinally follow patients for multiple cardiovascular outcomes.

One of the most important contributions of this study to the current literature is a comparison of renal outcomes among women and men with incident hypertension. We found that women were 17% more likely to develop chronic kidney disease, based on ICD-9 codes or eGFR, than men. These findings were further supported by our secondary analysis among patients matched on baseline age and eGFR. In this matched subgroup, women remained significantly more likely to have lower eGFR and had faster rates of eGFR decline over follow up compared to men. Our findings are similar to a few randomized trials and large registries among hypertensive patients which suggested a faster decline in renal function among women compared to men.[11, 22] Hanratty et al. also showed an association between female gender and the development of incident chronic kidney disease among a prevalent hypertensive population from Kaiser Colorado alone.[23] Conversely, other studies in hypertension populations have found either no difference or an overall slower decline in renal function among women compared to men.[9, 10, 12, 24] A possible explanation for this conflicting data is related to differences in the populations studied and variation in how incident chronic kidney disease was defined.[25] Bash and colleagues have shown that the directionality of gender differences in incident chronic renal disease estimates is highly dependent on the definition used. A definition based on eGFR showed women had a higher incidence of chronic renal disease than men, whereas a creatinine-based definition showed women had a lower incidence of chronic renal disease compared to men. [25] We defined incident chronic renal disease based on diagnostic codes and eGFR in order to account for gender differences in muscle mass which are reflected in creatinine levels. Further, even mild reductions in eGFR are associated with a higher risk for poor outcomes compared to those with normal eGFR and therefore, we opted to define CKD based on eGFR.[26, 27] Our findings highlight the importance of closely monitoring renal function

among women with incident hypertension given their potentially greater risk for adverse renal outcomes.

Similar to other studies, we found that the adjusted risk of all-cause death associated with hypertension was higher in men compared to women.[1, 6, 28] Yet, despite an overall lower risk of death among women, other studies have shown that the proportion of total mortality in patients with high blood pressure is greater in women compared to men (56.9% vs. 43.1%), largely related to the higher prevalence of hypertension in women.[1] In addition, a Finnish study reported the population attributable fraction, or excess risk of death attributed to isolated systolic hypertension was significantly higher for middle aged women compared to middle aged men suggesting the theoretical benefit to eliminating hypertension in women may be greater than in men.[6] Furthermore, our group and others have shown that hypertension treatment and control, particularly among older age groups, is lower in women compared to men.[29, 30] Therefore, continued efforts to improve blood pressure recognition, treatment and control in women and men remains important from a public health perspective.

In regards to the other cardiovascular outcomes assessed in this study, women with incident hypertension were found to be less likely to suffer a subsequent MI or stroke and equally likely to be admitted for HF compared to men. In regards to MI and HF, our findings are similar to Lloyd-Jones et al who conducted one of the few US studies comparing longitudinal cardiovascular events in those with incident hypertension using the Framingham cohort.[8] However, this same study found similar stroke rates between men and women (5.3% vs. 5.8%) with incident hypertension over 12 years of follow-up. An international study also found similar rates of subsequent stroke and MI in men and women with hypertension.[31] A possible reason for the outcome differences in the current study and prior work include alternative definitions of hypertension. Prior studies have commonly used higher levels of elevated blood pressure (SBP $\geq$ 160 mm Hg and DBP $\geq$ 95–100 mm Hg) to define baseline hypertension.[6, 8, 32] Our lower blood pressure cutoffs to define hypertension are based on current clinical guidelines and may have resulted in cohort at overall lower risk for subsequent events compared to cohorts using higher blood pressure cutoffs. Moreover, our cohort is more contemporary than many prior studies, so that lower event rates may reflect clinical improvements in blood pressure treatment and control resulting in lower cardiovascular events rates for both men and women. Our observed mortality rates could also be affected by recent advances in clinical management of those who have acute cardiovascular events. Future studies in contemporary cohorts with incident hypertension should assess whether cardiovascular outcomes are similar over longer periods of follow-up using currently defined hypertension cutoffs among women and men.

Certain factors should be considered in the interpretation of these results. First, this study relies on blood pressure measurements from an electronic medical record to define hypertension. However, we have shown that the algorithms used to identify hypertensive patients were valid and the analytic data accurately reflect the data in the charts.[20] Further, the definition of hypertension was equally applied to men and women and office based blood pressure measurements reflect current practice routinely used in the diagnosis of hypertension. Second, study follow-up was relatively short in duration compared to other longitudinal studies evaluating hypertension outcomes. However, with over 550,000 person-years of follow up, this is one of the largest contemporary cohort studies investigating hypertension outcomes among a clinical population of women and men with incident hypertension. Third, we relied on estimating GFR from the MDRD study equation rather than using a direct method of measuring GFR. Despite its limitation, the MDRD equation is the most widely used prediction equations in clinical practice and can be easily calculated from factors widely available in the clinical record.[21] In addition, we were not able to

determine how many men and women who met our criteria of incident chronic kidney disease (based on diagnostic codes or a eGFR decline) had other evidence for renal dysfunction such as micro or macroalbuminuria. Similarly, we were unable to account for menopausal status. Finally, findings observed in these healthcare systems may not be generalizable to other healthcare settings. Nevertheless, these systems care for more than 4 million patients with hypertension in geographically distinct areas of the country.

Overall, the findings of this study have a number of important implications for investigation and clinical care. First, we have demonstrated that the rates of cardiovascular complications among men and women with incident hypertension are relatively low in the first 3 years after identification. However, the differences in event rates between our study and other longitudinal cohorts highlight the importance of long term follow-up, likely at least a decade, when comparing incident cardiovascular events in an incident hypertensive population.[32] Second, compared to women, men with incident hypertension are at higher risk for most cardiovascular outcomes. Understanding reasons for this increased risk is important for targeting interventions to improve hypertension outcomes among men. Third, compared to men, women with incident hypertension are at higher risk for worsened renal function suggesting a need for closer monitoring and focused preventive efforts on preserving renal function among women with hypertension. Future studies should investigate causes of these gender differences in order to improve cardiovascular outcomes for women and men.

Conclusion

In this cohort of patients from 3 healthcare systems with incident HTN, women were more likely to subsequently develop chronic kidney disease but less likely to develop other cardiovascular outcomes compared to men. Future studies should investigate factors that may explain these gender differences in cardiovascular outcomes.

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		Baseline	1yr	2yr	3yr	4yr	5yr	6yr	7yr
Women	N	40312	22296	21234	17876	14366	9918	5039	851
	Mean*	82.84	81.42	79.46	76.89	75.17	74.08	73.80	72.82
	SD	17.99	20.37	20.22	19.67	19.34	19.57	20.01	20.68
Men	N	40312	21744	18823	14768	10605	6280	2515	255
	Mean*	83.42	81.59	79.87	78.04	76.78	76.11	75.54	75.11
	SD	17.21	19.44	18.84	18.63	18.49	18.81	19.12	21.47

* $p < 0.02$ for comparison of mean eGFR at each year; adjusted for clinical characteristics and repeated eGFR measures over time

**Slope for women = -1.61, slope for men = -1.38; $p < 0.001$ for comparison

Figure 1.

Mean eGFR over time among men and women in the age and eGFR matched cohort

Table 1

Baseline study population characteristics.

Characteristic	Women (n=97,577)		Men (n=79,944)		p-value
	Median	(25%,75%)	Median	(25%,75%)	
Age	56	(47, 67)	53	(44, 62)	<0.001
Blood pressure at entry					
Systolic blood pressure	147	(146, 147)	147	(140, 147)	<0.001
Diastolic blood pressure	87	(70, 94)	87	(80, 94)	<0.001
No. of creatinine measurements	3	(1, 6)	2	(1, 6)	<0.001
Site	N	%	N	%	p-value
Kaiser Permanente Colorado	11,054	11.3%	10,233	12.8%	<0.001
Kaiser Northern California	82,826	84.9%	66,249	82.9%	
Health Partners Minnesota	3,697	3.8%	3,462	4.3%	
Race/Ethnicity					
White	55,782	57.2%	40,202	50.3%	<0.001
Black	7,587	7.8%	4,705	5.9%	
Hispanic	9,923	10.2%	7,347	9.2%	
Asian	9,094	9.3%	6,311	7.9%	
Other	1,642	1.7%	1,139	1.4%	
Unknown	13,549	13.9%	20,240	25.3%	
Body Mass Index					
< 18.5	242	0.5%	53	0.1%	<0.001
18.5 – 25	10,757	23.7%	5,754	14.5%	
25–30	13,757	30.3%	15,395	38.7%	
30	20,574	45.4%	18,539	46.6%	
Socioeconomic status					
High	74,997	76.9%	61,791	77.3%	<0.001
Low	19,855	20.3%	15,702	19.6%	
Unknown	2,725	2.8%	2,451	3.1%	
History of:					
Chronic kidney disease	8,815	9.0%	5,452	6.8%	<0.001

<u>Characteristic</u>	<u>Women</u> (n=97,577)		<u>Men</u> (n=79,944)		<u>p-value</u>
	<u>Median</u>	<u>(25%,75%)</u>	<u>Median</u>	<u>(25%,75%)</u>	
Diabetes mellitus	12,759	13.1%	14,642	18.3%	<0.001
Coronary artery disease	577	0.6%	1,129	1.4%	<0.001
Myocardial infarction	80	0.1%	99	0.1%	0.006
Congestive heart failure	147	0.2%	140	0.2%	0.202
Peripheral vascular disease	348	0.4%	493	0.6%	<0.001
Cerebral vascular disease	1,065	1.1%	878	1.1%	0.891
Ulcer	2,476	2.5%	1,759	2.2%	<0.001
Cancer	15,698	16.1%	9,610	12.0%	<0.001
Depression	9,897	10.1%	4,103	5.1%	<0.001
Dementia	638	0.7%	320	0.4%	<0.001
Connective tissue disease	1,615	1.7%	452	0.6%	<0.001
Thyroid disease	6,757	6.9%	1,459	1.8%	<0.001
Chronic obstructive pulmonary disease	603	0.6%	432	0.5%	0.03
Asthma	7,417	7.6%	3,913	4.9%	<0.001

Table 2

Incidence of cardiovascular outcomes by gender

All-cause Death	# of patients	Incident cases	Person -years	Incidence rate [*]	Unadjusted HR [^] (95% CI)	Adjusted HR ^{^,†} (95% CI)
Total cohort [‡]	177521	7669	579243	13.24	0.96, (0.92, 1.00)	0.85, (0.80, 0.90)
Women	97577	4283	329166	13.01		
Men	79944	3386	250078	13.54		
Chronic Kidney Disease						
Total cohort [‡]	168033	14267	551661	25.86	1.25, (1.21, 1.30)	1.17, (1.12, 1.22)
Women	91805	8815	312323	28.22		
Men	76228	5452	239338	22.78		
Myocardial Infarction						
Total cohort [‡]	177342	1883	578584	3.25	0.44, (0.40, 0.48)	0.44, (0.40, 0.48)
Women	97497	697	328877	2.12		
Men	79845	1186	249707	4.75		
Stroke						
Total cohort [‡]	175578	1617	572448	2.82	0.76, (0.69, 0.84)	0.68, (0.60, 0.76)
Women	96512	814	325399	2.50		
Men	79066	803	247049	3.25		
Congestive Heart Failure						
Total cohort [‡]	177234	882	578294	1.53	0.89, (0.78, 1.02)	0.90, (0.76, 1.07)
Women	97430	481	328672	1.46		
Men	79804	401	249623	1.61		

^{*} Incidence per 1000 person years of follow-up[‡] Denominator for each event excludes those with a history of that event[^] Women versus Men

[†] Adjusted for year of cohort entry, study site, baseline blood pressure, baseline creatinine, and patient characteristics (gender, race, age, socioeconomic status, weight status and history of diabetes mellitus, peripheral vascular disease, asthma, cancer, connective tissue disease, chronic obstructive pulmonary disease, dementia, depression, hyperlipidemia, liver disease, thyroid disease, and peptic ulcer disease).