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Left ventricular hypertrophy offsets the sex difference in cardiovascular risk (the Campania Salute Network)☆

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ABSTRACT

Background: In general, women have lower risk for cardiovascular disease. We tested whether this sex-specific protection persists also in the presence of hypertensive left ventricular hypertrophy (LVH).
Methods: 12,329 women and men with hypertension and free from prevalent cardiovascular disease enrolled in the prospective Campania Salute Network registry were followed over a median of 4.1 years. Subjects were grouped according to the absence or the presence of LVH identified by echocardiography using validated sex-specific cut-off values of LV mass index (>47 g/m$^{2.7}$ in women and >50 g/m$^{2.7}$ in men). Main outcome was major cardiovascular events (MACE; combined **a**cute coronary syndromes, stroke, hospitalization for heart failure and incident atrial fibrillation).
Results: The cardiovascular risk profile accompanying LVH did not differ between sexes, but presence of obesity and diabetes carried higher probability for LVH in women, and LVH was more prevalent in women than men (43.4 vs. 32.1%, $p < 0.001$). Among patients without LVH ($n = 7764$), women had a 35% lower hazard rate (HR) for MACE ($n = 179$) than men (95% confidence interval [CI] 0.44–0.96, $p = 0.031$) in Cox regression analysis adjusting for cardiovascular risk factors and antihypertensive treatment during follow up. In contrast, among patients with LVH ($n = 4565$), women had a similar HR for MACE as men (HR 0.94 [95% CI 0.69–1.30], $p = 0.720$).
Conclusion: This study demonstrates that presence of LVH in hypertension offsets the female sex-protection in cardiovascular risk. Thus among hypertensive subjects with LVH, women and men have comparable cardiovascular risk.

1. Introduction

Sex-differences in epidemiology, pathophysiology, clinical presentation, effect of therapy or outcome have been reported for most major cardiovascular (CV) diseases [1]. It is well demonstrated that women in general have a lifelong lower incidence of CV disease than men, in particular of coronary artery disease and acute coronary syndromes [2–3]. However, atrial fibrillation, stroke and heart failure become more common in women with advancing age [1,4–6], paralleling the increasing prevalence of hypertension in elderly women [7–8].

Hypertensive women exhibit higher prevalence of subclinical cardiac damage, such as left ventricular (LV) hypertrophy (LVH) [9]. This may in part be explained by the greater influence of visceral obesity on LV mass and geometry in women than men, as documented both in studies using echocardiography and cardiac magnetic resonance imaging [10–11]. Presence of LVH both in general population and in hypertension strongly predisposes to clinical major cardiovascular events (MACE) [12–13]. However, whether presence of LVH in hypertension offsets the sex difference in CV risk is currently unknown. Accordingly, the present study was undertaken to assess the impact of the absence or presence of LVH on prognosis in women and men with arterial hypertension.

2. Methods

2.1. Patient population

The Campania Salute Network is an open electronic registry networking 23 community hospital-based hypertension clinics, and 60 general practitioners from the Campania district in Southern Italy to the Hypertension Research Center of Federico II University Hospital in Naples (Clinical Trials identifier NCT02211365) [14–15]. Subjects recruited

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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by participating hospitals or general practitioners are referred for CV imaging at the Hypertension Research Center, but otherwise managed by their primary health care physician [16–17]. A total of 15,000 hypertensive patients are currently included in the Campania Salute Network. For the present study patients with prevalent CV disease ($n = 284$) or without a readable echocardiogram ($n = 1386$) at the baseline study visit were excluded, leaving a total of 12,329 patients (5392 women and 6937 men) with treated hypertension for the present analysis.

The study protocol of the Campania Salute Network conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Institutional Ethic Committee of Federico II University Hospital. All participants signed written informed consent for the possibility of using the data for scientific purposes.

2.2. CV risk factor assessment

Prevalent CV disease was identified at the first examination in the outpatient clinic and included previous myocardial infarction, angina pectoris, coronary revascularization procedures, stroke, transitory ischemic attack, or congestive heart failure [16–17]. Clinic blood pressure (BP) was measured in triplets by regularly calibrated aneroid sphygmomanometers after at least 5 min of rest in the sitting position, following current guidelines [18]. The average of the two last measurements was taken as the clinic BP. Obesity was defined as a body mass index (BMI) ≥ 30 kg/m^2. Fasting glucose, lipid profile and serum uric acid (SUA) were measured by standard methods. High SUA was defined as the upper tertile of the SUA distribution in the population. Diabetes was defined as history of diabetes, use of any anti-diabetic medication or presence of a fasting blood glucose >7.0 mmol/L [19].

2.3. Echocardiography

Echocardiography was performed using commercially available phased-array machines following a standardized protocol. Quantitative measurements were obtained off-line by a single highly experienced reader and quality assured by a senior faculty member, in accordance with the joint European Association of Echocardiography and American Society of Echocardiography recommendations [20]. LVH was identified by the prognostically validated sex-specific cut-off values for LV mass/height$^{2.7}$, >47 g/m$^{2.7}$ in women and >50 g/m$^{2.7}$ in men, respectively [21]. Relative wall thickness was calculated as the ratio between posterior wall thickness and LV internal radius at end-diastole and considered increased if ≥0.43.

2.4. Endpoints

Incident MACE was adjudicated by the Committee for Event Adjudication in the Hypertension Research Center [15–16]. Incident MACE included combined acute coronary syndromes, stroke, hospitalization for heart failure and incident atrial fibrillation. Event adjudication was based upon patient history, contact with the reference general practitioner, and review of hospital medical records [15–17].

2.5. Statistical analysis

Statistical analyses were done using IBM SPSS 23 (IBM Corporation, Armonk, NY, USA). Data are presented as mean ± standard deviation for continuous variables and as percentages for categorical variables. The study population was grouped according to sex and presence of LVH at the baseline study echocardiogram. Groups were compared using one-way analysis of variance for continuous variables and a general linear model with Sidak's posthoc test for categorical variables. Covariables of prevalent LVH were identified in sex-specific uni- and multivariable logistic regression analyses and reported as odds ratio (OR) and 95% confidence intervals (CI). To account for antihypertensive therapy during follow-up, single classes of medications were dichotomized according to their overall use during the individual follow-up, based on the frequency of prescriptions at the control visits during follow-up. All medications used at >50% of control visits in an individual patient were included in the antihypertensive therapy during follow-up covariate in the Cox analyses, a method that has been previously reported [16–17]. The impact of sex on incident MACE was tested in Cox regression analyses in the absence and presence of LVH. Results from Cox analyses were reported as hazard rates (HR) and 95% CI. Multivariable Cox models were adjusted for age, systolic BP, diastolic BP, obesity, serum total cholesterol, uric acid and creatinine, smoking, diabetes mellitus, LV ejection fraction, and number of antihypertensive drugs during follow-up. A two-tailed p-value <0.05 was considered statistically significant in all analyses.

3. Results

3.1. Sex differences in CV risk factors in absence and presence of LVH

Irrespective of presence of LVH, women were older and had higher systolic BP, total and high-density lipoprotein cholesterol, and lower diastolic BP, serum triglycerides, uric acid and creatinine (all $p < 0.01$) (Table 1).

Among patients with LVH, women had higher prevalence of obesity and lower prevalence of smoking than their male counterparts (all $p < 0.05$) (Table 1). The number of antihypertensive drugs did not differ by sex, but was higher than in subjects without LVH (Table 1). β-Blockers and diuretics were more commonly used in

Table 1
Characteristics in women and men without and with LVH at the baseline visit.

Variables	Subjects without LVH		Subjects with LVH	
	Women ($n = 3053$)	Men ($n = 4711$)	Women ($n = 2339$)	Men ($n = 2226$)
Age (years)	51 ± 12*	48 ± 13	59 ± 11*,†	56 ± 11†
Systolic BP (mm Hg)	142 ± 18*	141 ± 16	149 ± 22†	149 ± 20†
Diastolic BP (mm Hg)	87 ± 11*	88 ± 11	88 ± 12*,†	90 ± 12†
Heart rate (bpm)	74 ± 12*	73 ± 12	73 ± 12*,†	71 ± 12†
Number of antihypertensive drugs	0.9 ± 1.0	0.9 ± 1.0	1.3 ± 1.2†	1.2 ± 1.1†
ACEI (%)	22.5	21.1	26.0†	29.3†
ARB (%)	17.0	16.9	23.1†	21.1†
CCB (%)	12.6*	15.8	21.7*,†	27.2†
Beta-blocker (%)	19.4*	14.8	23.5*,†	19.6†
Alpha-blocker (%)	4.1	4.9	6.6*,†	11.2†
Alpha-beta blocker (%)	2.2	2.4	3.8†	3.2
Diuretics (%)	22.1*	18.4	33.1*,†	27.7
Body mass index (kg/m^2)	26.1 ± 4.3*	27.3 ± 3.4	29.7 ± 5.0*,†	29.3 ± 4.1†
Obesity (%)	15.6*	18.7	40.6*,†	36.5†
Diabetes (%)	5.5*	7.2	14.9†	14.0†
Current smoking (%)	19.4	20.7	13.8*,†	17.2
Serum total cholesterol (mg/dL)	211 ± 39*	201 ± 39	213 ± 40*	200 ± 38
Serum HDL-cholesterol (mg/dL)	57 ± 14*	47 ± 11	54 ± 13*,†	46 ± 12
Serum triglycerides (mg/dL)	117 ± 64*	142 ± 81	133 ± 75*,†	145 ± 78†
Serum creatinine (mg/dL)	0.83 ± 0.19*	1.03 ± 0.19	0.88 ± 0.28*,†	1.08 ± 0.31†
Serum uric acid (mg/dL)	4.4 ± 1.3*	5.6 ± 1.4	4.8 ± 1.4*,†	5.8 ± 1.5†
LV end-diastolic diameter (cm)	4.67 ± 0.25*	5.03 ± 0.28	4.93 ± 0.30*,†	5.32 ± 0.36†
LV end-diastolic diameter index (cm/m)	2.88 ± 0.15	2.89 ± 0.15	3.11 ± 0.18*,†	3.14 ± 0.19†
LV mass/height$^{2.7}$ (g/m$^{2.7}$)	40.1 ± 4.7*	41.9 ± 5.1	55.1 ± 7.4*,†	57.7 ± 7.9†
Relative wall thickness	0.38 ± 0.04	0.38 ± 0.03	0.39 ± 0.04†	0.39 ± 0.04†
LV ejection fraction (%)	68 ± 4*	67 ± 3	66 ± 4*,†	64 ± 5†

LVH, left ventricular hypertrophy; BP, blood pressure; bpm, beats per minute: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; HDL, high-density lipoprotein; LV, left ventricular.

* $P < 0.01$ vs. men.

† $P < 0.01$ vs. same sex without LVH.

women, while calcium channel blockers, angiotensin converting enzyme inhibitors and α-blockers were more commonly used in men (all $p < 0.01$) (Table 1). In contrast, among patients without LVH, women had lower BMI and lower prevalence of diabetes than men (both $p < 0.01$) (Table 1). The number of antihypertensive drugs did not differ between sexes, but β-blockers and diuretics were more commonly used in women, while calcium channel blockers were more commonly used in men (all $p < 0.01$) (Table 1).

LVH was more prevalent in women than in men (43.4 vs. 32.1%, $p < 0.01$) and associated with lower LV ejection fraction in both sexes (Table 1). Women also had higher LV ejection function than men irrespective of presence of LVH (Table 1).

3.2. Covariables of LVH in women and men

The general risk profile accompanying LVH did not differ between women and men, but presence of obesity and diabetes carried higher probability for LVH in women than men, and higher serum triglycerides and uric acid were both associated with LVH in women but not in men (Table 2).

3.3. CV prognosis in the absence and presence of LVH

In Cox regression analysis among patients without LVH, adjusting for the age-difference between sexes, women had a 31% lower HR for MACE ($n = 176$) (95% CI 0.50–0.95, $p = 0.023$), while among subjects with LVH the sex-difference in HR for MACE ($n = 202$) disappeared (HR 0.80 for women [95% CI 0.60–1.05], $p = 0.108$). The findings became even more striking after further adjustment for sex-differences in CV risk factors, including presence of obesity and diabetes, current smoking, systolic and diastolic BP, serum creatinine, uric acid and total cholesterol, LV systolic function at baseline and antihypertensive treatment during follow-up (Table 3) (Fig. 1).

4. Discussion

4.1. Sex, LVH and outcome

The present analysis, from a large prospective registry of subjects with hypertension, reflecting real world practice, is the first to document that the general lower CV risk in women is offset in hypertension when LVH is present. The findings expand previous knowledge from general population and clinical trials on the prognostic impact of LVH in women with hypertension [12,22]. As demonstrated, the HR for MACE was significantly lower in women than men when LVH was not present, in line with previous findings in the general population. However, presence of LVH offset this sex difference in CV risk. Of note, this finding persisted after adjustment for CV risk factors as well as for LV systolic function and antihypertensive treatment during follow-up. Accordingly, extrapolating this finding, we may say that LVH seems to be more harmful in women than in men.

Our results contrast a previous report from the Losartan Intervention For Endpoint reduction in hypertension (LIFE) trial [22]. The LIFE trial was carried out in subjects with hypertension selected on the basis of presence of signs of LVH on the electrocardiogram [22]. In LIFE, incident CV death, stroke and myocardial infarction was 35% lower in women than in men [22], independent of treatment randomization and despite less treatment-induced reduction of LVH in women [9]. The diverging results are probably explained by differences in study population characteristics. In particular, the LIFE study included a higher proportion of men than women with prevalent CV and cerebrovascular disease [22], while in the present study population subjects with prevalent CV disease had been excluded.

Interestingly, despite exclusion of subjects with prevalent CV disease from the present analysis, lower LV ejection fraction was associated with higher HR for MACE in subjects without LVH, possibly reflecting subclinical coronary artery disease [23]. Among subjects with LVH, higher systolic BP, lower diastolic BP and renal dysfunction were all independent predictors of incident MACE, probably related to more advanced arterial damage and higher arterial stiffness. In hypertensive patients with LVH, presence of isolated systolic hypertension and higher arterial stiffness have both been identified as high risk markers and associated with impaired outcome [24–25].

4.2. Covariables of LVH in women and men

As demonstrated, concomitant diabetes and obesity were both associated with higher risk for prevalent LVH in women than men. From the Framingham Heart Study, a larger relative impact of diabetes for coronary heart disease mortality in women compared to men was reported [26]. In a meta-analysis, Peters et al. found that women with type 2 diabetes had a 40% higher risk for incident coronary heart disease [27]. In the Campania Salute Network registry, presence of LVH has previously been documented as a strong predictor of incident diabetes mellitus [16]. Taken together, the current results demonstrate that presence of hypertensive LVH offsets the sex difference in CV risk, in line with what has previously been demonstrated for diabetes [28]. Thus, the present findings are of potential importance for future guidelines on CV disease prevention.

Obesity is documented as a main factor associated with reduced cardiac benefit from antihypertensive treatment, and subsequent higher CV event rate [29–30]. The differential influence of obesity on target organ damage in hypertension was recently demonstrated by Mancusi et al. [31], finding obesity to be associated with a pronounced increase in prevalent LVH, but only with a modestly increased prevalence of carotid atherosclerosis. Adding to previous publications, the present study found obesity as a covariate of LVH in both sexes, but particularly strong in women [10]. However, when LVH was taken into account, obesity was not anymore an independent predictor of incident MACE in either sex.

High SUA may influence LV mass through angiotensin receptor mediated inflammation [32]. As demonstrated, high SUA was an independent covariate of LVH in both sexes, expanding previous observations in subjects with hypertension [33]. In the LIFE study, Høieggen et al. demonstrated that higher SUA was associated with increased HR of combined sudden cardiac death and nonfatal myocardial infarction and stroke in women with LVH, but not in men [34]. However, in the present study, no independent association between high SUA and incident MACE was found in adjusted Cox regression analyses. In contrast,

Table 2
Covariables of LVH in women and men in univariable and multivariable logistic regression analyses including all displayed covariables.

	Univariable		Multivariable	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Women				
Age (years)	1.06 (1.06–1.07)	<0.001	1.06 (1.05–1.07)	<0.001
Obesity	3.70 (3.26–4.21)	<0.001	4.23 (3.60–4.97)	<0.001
Diabetes	3.01 (2.48–3.65)	<0.001	1.81 (1.40–2.32)	<0.001
Systolic BP (mm Hg)	1.02 (1.01–1.02)	<0.001	1.02 (1.01–1.02)	<0.001
Serum creatinine (mg/dL)	2.54 (1.85–3.49)	<0.001	1.33 (0.96–1.83)	0.088
Triglycerides (10 mg/dL)	1.04 (1.03–1.05)	<0.001	1.03 (1.02–1.04)	<0.001
High SUA	1.26 (1.21–1.31)	<0.001	1.09 (1.03–1.15)	0.004
Men				
Age (years)	1.06 (1.05–1.06)	<0.001	1.06 (1.05–1.06)	<0.001
Obesity	2.49 (2.22–2.79)	<0.001	2.87 (2.49–3.29)	<0.001
Diabetes	2.09 (1.78–2.46)	<0.001	1.27 (1.04–1.55)	0.022
Systolic BP (mm Hg)	1.02 (1.01–1.03)	<0.001	1.02 (1.01–1.03)	<0.001
Serum creatinine (mg/dL)	2.25 (1.74–2.90)	<0.001	1.53 (1.17–2.01)	0.002
Triglycerides (10 mg/dL)	1.01 (0.99–1.02)	0.141	n.a.	
High SUA	1.09 (1.05–1.13)	<0.001	1.04 (0.99–1.08)	0.141

OR, odds ratio; CI, confidence interval; BP, blood pressure; SUA, serum uric acid. n.a., not applicable.

Table 3
The association of female sex with incident MACE in multivariable Cox regression models among with and without left ventricular hypertrophy.

Variables	Subjects without LVH		Subjects with LVH	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Female sex	0.65 (0.44–0.96)	0.031	0.94 (0.69–1.30)	0.720
Age (years)	1.05 (1.03–1.07)	<0.001	1.05 (1.03–1.07)	<0.001
Systolic BP (mm Hg)	1.00 (0.99–1.01)	0.536	1.02 (1.01–1.03)	<0.001
Diastolic BP (mm Hg)	1.00 (0.98–1.02)	0.980	0.98 (0.96–0.99)	0.001
Obesity	1.32 (0.87–2.00)	0.185	0.90 (0.66–1.24)	0.528
Serum total cholesterol (mg/dL)	1.00 (0.99–1.01)	0.957	1.00 (0.99–1.00)	0.784
Current smoking	1.37 (0.93–2.03)	0.109	1.07 (0.67–1.69)	0.785
Diabetes mellitus	1.53 (0.93–2.53)	0.094	1.06 (0.71–1.58)	0.776
Serum creatinine (mg/dL)	0.66 (0.27–1.64)	0.374	1.71 (1.09–2.68)	0.020
Serum triglycerides (mg/dL)	1.00 (0.97–1.02)	0.777	1.02 (1.01–1.04)	0.019
High SUA	1.07 (0.76–1.52)	0.702	0.91 (0.67–1.24)	0.558
LV ejection fraction (%)	0.95 (0.92–0.99)	0.027	0.95 (0.92–0.98)	<0.001
Number of antihypertensive drugs during follow-up	1.26 (0.93–2.53)	0.007	1.14 (0.98–1.31)	0.083

LVH, left ventricular hypertrophy; HR, hazard ratio; CI, confidence interval; BP, blood pressure; SUA, serum uric acid; LV, left ventricular.

higher serum triglycerides were associated with LVH only in women, in line with previous observations in the Strong Heart Study [10], and associated with higher HR of MACE in subjects with LVH, independent of sex and other cardiometabolic risk factors including obesity, diabetes and SUA.

5. Conclusion

The present study is the first to document that the lower CV risk in women with hypertension is offset when LVH is present. The results warrant increased attention to diagnosis and management of LVH to help reduce CV disease in these high-risk women.

6. Study limitations

The Campania Salute Network registry is a prospective observational study of subjects with hypertension. Since all participants are Caucasians, generalization of results to women of other races should be done with caution. Yet, one of the advantages of observational studies compared to controlled studies is the generation of results in a real-world context, which allows generalization and provides external validation for clinical trials [35].

In the present study, baseline blood pressure was measured by manual aneroid sphygmomanometers, which are not considered as accurate as the modern automated devices. However, the Campania Salute Network was initiated at a time when the use of automated devices was uncommon.

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Disclosures

The authors report no relationships that could be construed as a conflict of interest.

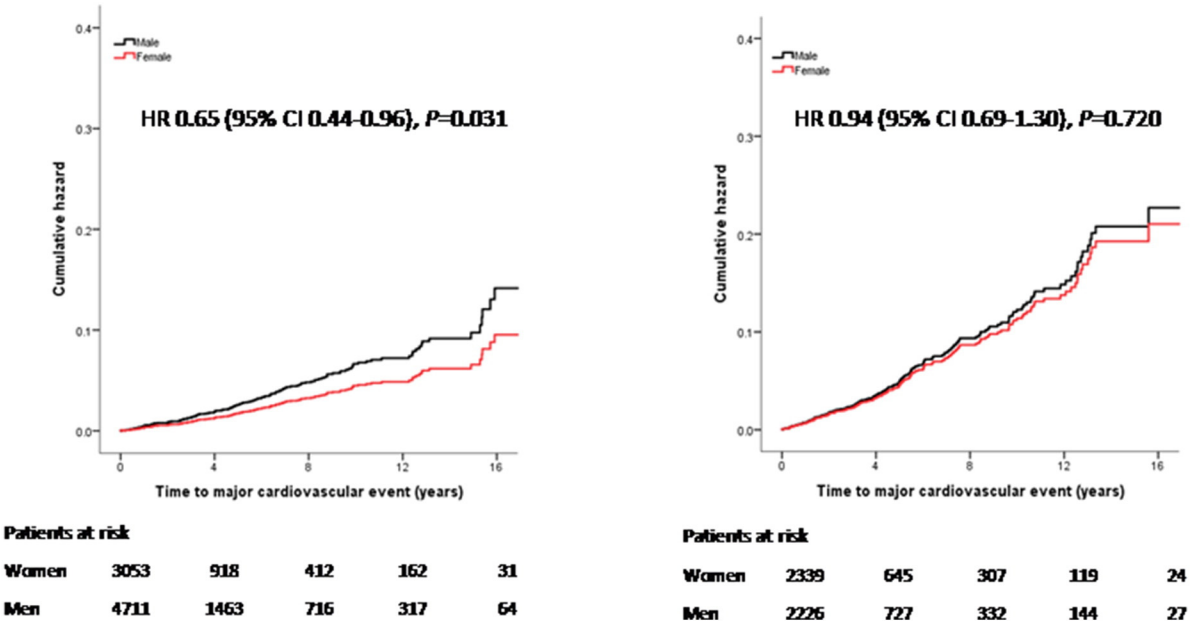

Fig. 1. Women had lower hazard rate of major cardiovascular events than men when left ventricular hypertrophy was absent (panel A), but not when left ventricular hypertrophy was present (panel B).

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