Effect of Systemic Hypertension With Versus Without Left Ventricular Hypertrophy on the Progression of Atrial Fibrillation (from the Euro Heart Survey)

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Hypertension is a risk factor for both progression of atrial fibrillation (AF) and development of AF-related complications, that is major adverse cardiac and cerebrovascular events (MACCE). It is unknown whether left ventricular hypertrophy (LVH) as a consequence of hypertension is also a risk factor for both these end points. We aimed to assess this in low-risk AF patients, also assessing gender-related differences. We included 799 patients from the Euro Heart Survey with nonvalvular AF and a baseline echocardiogram. Patients with and without hypertension were included. End points after 1 year were occurrence of AF progression, that is paroxysmal AF becoming persistent and/or permanent AF, and MACCE. Echocardiographic LVH was present in 33% of 379 hypertensive patients. AF progression after 1 year occurred in 10.2% of 373 patients with rhythm follow-up. In hypertensive patients with LVH, AF progression occurred more frequently as compared with hypertensive patients without LVH (23.3% vs 8.8%, p = 0.011). In hypertensive AF patients, LVH was the most important multivariably adjusted determinant of AF progression on multivariable logistic regression (odds ratio 4.84, 95% confidence interval 1.70 to 13.78, p = 0.003). This effect was only seen in male patients (27.5% vs 5.8%, p = 0.002), while in female hypertensive patients, no differences were found in AF progression rates regarding the presence or absence of LVH (15.2% vs 15.0%, p = 0.999). No differences were seen in MACCE for hypertensive patients with and without LVH. In conclusion, in men with hypertension, LVH is associated with AF progression. This association seems to be absent in hypertensive women. **(Am J Cardiol 2018;00:1–6)**

Atrial fibrillation (AF) is associated with several co-morbidities, the most prevalent being hypertension, affecting 49% to 90% of AF patients.[1] Hypertension is a risk factor for both the development[2] and the progression of AF.[3,4] Moreover, hypertension is a risk factor for the development of AF-related complications, such as major adverse cardiac and cerebrovascular events (MACCE).[5] Paroxysmal AF progresses to persistent or permanent AF in 8.6% to 22% of patients after 1 year, depending on the underlying co-morbidities.[6,7] AF progression is not merely an arrhythmic phenomenon, but it is also associated with a higher rate of ischemic stroke, that is 2% to 4% per year for paroxysmal, persistent and permanent AF, respectively.[8] Furthermore, AF progression has been associated with hospitalization and all-cause mortality in a primary care study.[9] Although the relation of hypertension with AF progression and MACCE is clearly established, it is unknown whether hypertensive end organ damage, that is left ventricular hypertrophy (LVH), is also associated with these end points and whether this differs across gender. We hypothesized patients with LVH as a result of hypertension show more AF progression and subsequent occurrence of MACCE compared with hypertensive AF patients without LVH and nonhypertensive patients. Furthermore, we aimed to investigate whether this differs across gender.

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This work was supported by the Netherlands Cardiovascular Research Initiative: an initiative with support of the Dutch Heart Foundation [CVON 2014-9, RACE V: "Reappraisal of Atrial Fibrillation: interaction between hyperCoagulability, Electrical remodeling, and Vascular destabilisation in the progression of AF" to Ö.E., M.R., I.C.V.G., H.J.G.M.C., and J.G.L.M.L].

See page 5 for disclosure information.

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https://doi.org/10.1016/j.amjcard.2018.04.053

Methods

A detailed description of the methods and results of the Euro Heart Survey (EHS) on AF has previously been published.[10,11] In summary, the EHS is a prospective registry conducted 2003 to 2005 in 182 hospitals across 35 member countries of the European Society of Cardiology. All centers obtained approval from their Institutional Committee on Human Research. Consecutive in and outpatients with (Holter) electrocardiogram proved AF were included after providing written informed consent. One-year follow-up was completed in 3,978 of the included 5,333 patients.

We included 799 patients from the EHS with nonvalvular, paroxysmal AF, and a baseline echocardiogram. Patients with and without hypertension were selected. Since we aimed to assess the relation of hypertension and LVH with the end points of AF progression and MACCE, we tried to diminish the influence of other factors related to these end points as much as possible. This was done by excluding patients with other stroke risk factors, that is congestive heart failure, age $\geq$65 years, diabetes mellitus, previous stroke and/or transient ischemic attack, and vascular disease.

The occurrence of AF progression and MACCE after 1 year was assessed separately for the groups with and without hypertension, subdivided by the presence of echocardiographic LVH. Gender differences were also evaluated. Hypertension was defined as the presence of systolic blood pressure (BP) at rest of $>$140 mm Hg or diastolic BP of $>$90 mm Hg on $\geq$2 occasions or current antihypertensive drug treatment. The presence or absence of echocardiographic LVH was assessed by the treating physician. AF progression was defined as paroxysmal AF at baseline becoming persistent or permanent AF after 1 year of follow-up, like previously defined by de Vos et al[4] and MACCE was defined as cardiovascular death, stroke, transient ischemic attack, systemic thromboembolism, myocardial infarction, or major bleeding (hemorrhagic stroke or bleeding requiring hospitalization, causing a hemoglobin level decrease of 2 g/l or requiring blood transfusion). Patients with missing data were excluded and a complete-case analysis was performed.

Data were analyzed with SPSS statistical software (version 22.0, SPSS Inc., Chicago, Illinois). Continuous variables are reported as mean $\pm$ standard deviation if normally distributed and as median and inter quartile range if not. Normally distributed continuous variables were compared between groups using the independent samples *t* test, whereas not normally distributed continuous variables were compared using the Mann−Whitney U test. Categorical variables are reported as observed number of patients and percentage. Amonggroup comparisons were made using a chi-square test. Fisher's exact test was used in case of any expected cell count $<$5. All baseline characteristics with a significant univariate association ($p < 0.10$) with one of the end points were incorporated into a multivariable logistic regression model with stepwise reduction of the model by excluding variables with $p > 0.10$. All variables in the final model were tested for interactions. Remaining variables with $p < 0.05$ were considered significant independent determinants for the end points of AF progression and the occurrence of MACCE.

Results

Of the 799 included patients, rhythm follow-up was available in 47% and information on the occurrence of MACCE in 76%. The majority of the patients was men (73%), mean age was 52 $\pm$ 10 years. AF progression occurred in 38 (10.2%) of 373 patients, whereas MACCE occurred in 21 (3.4%) of 610 patients. Hypertension was present in 47%. In general, hypertensive AF patients showed more AF progression (14.2% vs 7.1%, $p = 0.025$) as well as MACCE (5.3% vs 1.8%, $p = 0.018$), compared with the normotensives (Figure 1).

LVH was present in 124 (33%) of 379 hypertensive patients and in 51 (12%) of 420 normotensive AF patients. The baseline characteristics of the included patients, subdivided by the presence of hypertension and LVH, are presented in Table 1, together with the occurrence of the end points for all groups. In patients without hypertension, no differences in AF progression and in the development of MACCE could be ascertained when comparing patients with LVH to those without (Figure 2).

Hypertensive patients with echocardiographic LVH at baseline (124 of 379) had on average a higher body mass index and were more frequently on calcium antagonist and angiotensin converting enzyme inhibitors, compared with hypertensive patients without LVH (Table 1). AF progression at 1 year was significantly more prevalent in patients with LVH (23.3% vs 8.8%, $p = 0.011$), whereas no differences were found in the development of MACCE (4.5% vs 5.7%, $p = 0.782$; Figure 2).

Several determinants of AF progression were identified using multivariable analysis in the patients with hypertension, the most important being LVH on echocardiography (Table 2). Other independent determinants of AF progression were the use of vitamin K antagonists, age, and diastolic BP. No interactions were present. In hypertensive men, AF progression rates were 27.5% and 5.8% per year in those with and without LVH, respectively, similar to the rates seen in the studied overall cohort. In hypertensive women however, AF progression rates in patients with and without LVH did not differ, that is 15.2% versus 15.0%, $p = 0.999$ (Figure 3). Development of MACCE after 1 year did not differ between men with LVH vs without (3.2% vs 6.1%, $p = 0.507$), and in women (7.4% vs 5.0%, $p = 0.644$).

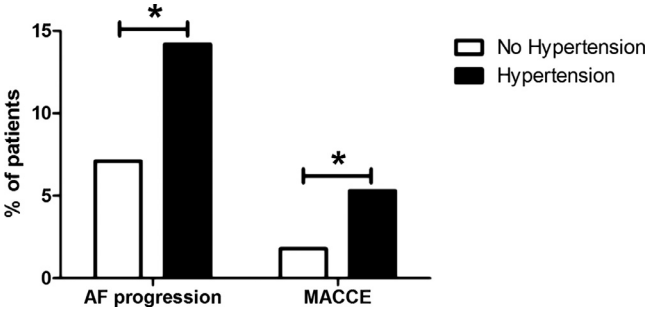

Figure 1. Differences in AF progression and MACCE rates after 1 year of follow-up for patients with and without hypertension.
AF = atrial fibrillation; MACCE = major adverse cardiac and cerebrovascular events.

Table 1
Baseline characteristics and the occurrence of end points for atrial fibrillation patients with and without hypertension, subdivided by the presence of left ventricular hypertrophy on echocardiography

Variable	Systemic hypertension					
	Yes (n = 379)			No (n = 420)		
	No LVH (n = 255)	LVH (n = 124)	p value	No LVH (n = 369)	LVH (n = 51)	p value
Age (years)	56 ± 8	55 ± 8	0.277	50 ± 11	52 ± 9	0.045
Women	80 (31%)	33 (27%)	0.342	94 (26%)	10 (20%)	0.363
Systolic blood pressure	142 ± 21	144 ± 23	0.388	125 ± 15	128 ± 16	0.281
Diastolic blood pressure	88 ± 13	88 ± 13	0.628	78 ± 10	79 ± 12	0.426
Ventricular rate on qualifying electrocardiogram	111 ± 33	109 ± 31	0.658	109 ± 31	108 ± 35	0.874
Body mass index (kg/m^2)	27.8 ± 4.2	28.9 ± 3.7	0.019	26.4 ± 3.9	28.0 ± 4.5	0.008
Left ventricular ejection fraction (%)	55 ± 13	53 ± 13	0.159	56 ± 13	56 ± 14	0.989
Left atrial diameter (mm)	42 ± 7	46 ± 8	0.001	41 ± 8	42 ± 10	0.449
Left atrial diameter index (mm/m^2)	22 ± 4	22 ± 3	0.253	21 ± 4	21 ± 5	0.858
Mitral regurgitation grade 2 and higher	68 (27%)	30 (24%)	0.606	61 (17%)	13 (26%)	0.115
Aortic regurgitation grade 2 and higher	21 (8%)	11 (9%)	0.843	14 (4%)	5 (10%)	0.067
Aortic stenosis*	3 (1.2%)	6 (4.8%)	0.064	2 (0.5%)	2 (3.9%)	0.074
Hyperlipidemia†	83 (34%)	35 (29%)	0.407	68 (19%)	13 (27%)	0.215
Valvular heart disease	17 (7%)	13 (11%)	0.213	28 (8%)	7 (14%)	0.171
Chronic obstructive pulmonary disease	17 (7%)	12 (10%)	0.285	10 (2.7%)	2 (3.9%)	0.647
Renal failure	4 (1.6%)	4 (3.2%)	0.448	0	1 (2.0%)	0.121
Hypothyroidism	13 (5.5%)	6 (5.3%)	0.946	11 (3.2%)	1 (2.0%)	0.999
Hyperthyroidism	15 (6.4%)	3 (2.7%)	0.141	19 (5.5%)	3 (6.1%)	0.745
Current smoker	47 (19%)	28 (23%)	0.302	87 (24%)	4 (8%)	0.009
Current alcohol drinker (≥1/week)	154 (64%)	65 (57%)	0.181	209 (62%)	26 (53%)	0.240
Medications						
Vitamin K antagonist	160 (65%)	70 (57%)	0.155	206 (60%)	26 (52%)	0.301
Beta blocker	29 (12%)	16 (13%)	0.736	12 (3.5%)	4 (8.0%)	0.131
Angiotensin converting enzyme inhibitor	129 (52%)	84 (68%)	0.004	43 (13%)	14 (28%)	0.003
Angiotensin receptor blockers	44 (18%)	21 (17%)	0.847	10 (2.9%)	1 (2.0%)	0.999
Dihydropiridine calcium channel blocker	25 (10%)	33 (27%)	0.001	5 (1.4%)	2 (4.0%)	0.218
Diuretic	82 (33%)	46 (37%)	0.440	24 (7%)	4 (8%)	0.768
Any anti-arrhythmic drug	148 (58 %)	64 (52%)	0.237	211 (57%)	34 (67%)	0.198
Atrial fibrillation progression at 1 year follow-up (n = 373)	9 (9%)	14 (23%)	0.011	13 (6.8%)	2 (9.5%)	0.649
Major adverse cardiac and cerebrovascular events at 1 year follow-up (n = 610)	11 (5.7%)	4 (4.5%)	0.782	5 (1.7%)	1 (2.9%)	0.494

* Aortic stenosis was defined as progressive narrowing of the aortic valve resulting in the obstructed passage of blood from the left ventricle into the aorta.
† Hyperlipidemia was defined as fasting total cholesterol >240 mg/dl (6.2 mmol/l) or LDL-cholesterol >160 mg/dl (4.1 mmol/l) or treatment with any lipid lowering drugs.

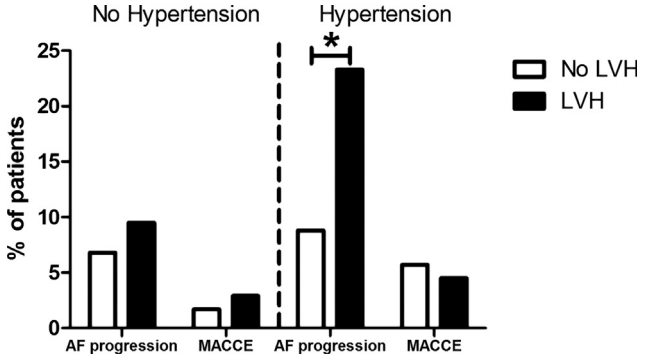

Figure 2. Differences in AF progression and MACCE rates after 1 year for patients with and without hypertension, subdivided by presence of LVH. AF = atrial fibrillation; LVH =l eft ventricular hypertrophy; MACCE = major adverse cardiac and cerebrovascular events. * = statistical significance.

In male patients with hypertension, the only independent determinant of AF progression was LVH (OR 6.16, 95% CI 1.81 to 20.99, p = 0.004). For female patients, independent determinants were age (OR 1.28 for increments of 1 year, 95% CI 1.02 to 1.61, p =0 .036), and diastolic BP (OR 0.93 for increments of 1 mm Hg, 95% CI 0.87 to 0.99, p = 0.029). In both hypertensive men and women, the use of VKA was not a determinant for AF progression, in contrast to the overall population. The difference between men and women who were prescribed vitamin K antagonists was statistically significant in the hypertensive patients (66% vs 53%, p = 0.017), but not in the normotensives (61% vs 53%, p = 0.178).

Discussion

Almost half of the patients in our cohort had a history of hypertension. These patients showed more often AF

Table 2
Univariable and multivariable regression for progression of atrial fibrillation in hypertensive patients

Variable	Univariable regression		Multivariable regression	
	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Left ventricular hypertrophy	3.15 (1.27-7.80)	0.013	4.84 (1.70-13.78)	0.003
Vitamin K antagonist	2.71 (1.04-7.08)	0.041	3.72 (1.28-10.83)	0.016
Age	1.11 (1.02-1.20)	0.016	1.13 (1.04-1.24)	0.007
Diastolic blood pressure, per mm Hg increase	0.96 (0.93-1.00)	0.058	0.95 (0.91-0.99)	0.017
Left atrial diameter, corrected for body surface area	1.12 (0.99-1.27)	0.076		

progression and MACCE after 1 year compared with patients without hypertension (Figure 1), in accordance with previous data.[3,5,12] LVH at baseline was present in a third of the patients with hypertension. As hypothesized, a significantly larger proportion of these patients showed AF progression after 1 year when compared with hypertensive patients without LVH on echocardiographic assessment (Figure 2). Recently, Padfield et al have also shown that LVH is one of the determinants of AF progression after a median follow-up of 6 years.[13] Moreover, the higher progression rate seen in patients with hypertension, could be mainly driven by LVH, since AF progression rates in hypertensive patients without LVH and nonhypertensive patients were comparable (Figure 2). Even after correcting for other factors, LVH remained the most important independent determinant of AF progression in the hypertensive group. Thus, LVH seems to be a key marker for AF progression in hypertensive patients with low-risk AF. However, a difference in the occurrence of MACCE could not be ascertained in these patients, possibly due to the overall low MACCE-rate in this relatively low-risk AF population and follow-up duration of 1 year. In addition, 60% of the patients were on vitamin K antagonists, probably reducing MACCE rates.[14]

It is unknown whether this effect of LVH on AF progression is reversible. Hennersdorf et al[15] have shown that the prevalence of paroxysmal AF can be diminished in patients with regression of LVH by treating hypertension, compared with patients with a progression in LVH despite treatment. In that post hoc analysis, 24-hour Holter electrocardiograms were performed at baseline and after a mean of 2 years of antihypertensive treatment. The short time span covered by these Holter electrocardiograms and the absence of a predefined scheme for rhythm follow-up, makes cautious interpretation of these data necessary. However, a similar reduction in AF progression rates could possibly be achieved by adequate treatment of hypertension leading to regression of LVH. Of course, this should be studied in a prospective and randomized manner to draw definite conclusions.

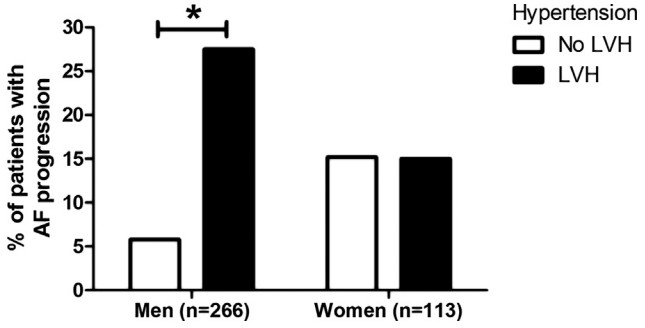

Figure 3. AF progression rates after 1 year of male and female hypertensive AF patients in absence and presence of LVH.
AF = atrial fibrillation; LVH = left ventricular hypertrophy.

Other independent determinants of AF progression in hypertensive AF patients were use of vitamin K antagonists, age, and diastolic BP. Age is a known risk factor for AF progression and is incorporated in the HATCH-score (Heart failure, Age, previous Transient ischemic attack or stroke, Chronic obstructive pulmonary disease, and Hypertension).[3,4] The use of VKA however is not a known risk factor for AF progression and the effect we observed may be due to confounding. Since stroke risk scores were not in use during the conduct of this registry, the decision to start antithrombotic therapy was made at the discretion of the treating physician. It is possible that this decision was based on clinical parameters, such as left atrial diameter, left atrial volume, and general health of the patient. An alternative explanation may be that VKA are known to cause vascular calcification in animal models.[16] Since coronary artery calcification in humans is associated with an increased risk of the development of AF, this process may also be associated with AF progression.[17]

The last independent determinant was diastolic BP. This effect has not been reported in literature before. Although it may be a chance finding, the protective effect of diastolic BP might in part be explained by the relatively higher pulse pressure in patients with a lower diastolic BP. Since a higher pulse pressure is indicative of stiffness of the aorta or major arteries and is related to vascular disease, it might play a role in the progression of AF. Pulse pressure is a known risk factor for new-onset AF, whereas in the same study mean arterial pressure was not related to incident AF.[18] Furthermore, pulse pressure, and not mean arterial pressure, was proved to be related to cardiovascular events in older hypertensive patients.[19] However, pulse pressure was not a significant determinant in our analysis.

In patients without hypertension, LVH was present in a smaller proportion and was not associated with AF progression and MACCE (Figure 2). These patients can be seen as truly low-risk AF, with an overall AF progression rate of 7.1% and a MACCE rate of 1.8% per year, both representing a fairly low risk. However, this could be partially caused by the small group of patients with LVH in the nonhypertensive patients. Perhaps in a larger population, LVH might lead to a higher AF progression rate through diastolic dysfunction and an increase in left atrial diameter, even in patients without hypertension.

With respect to progression of AF in male and female patients with hypertension, distinct differences were ascertained regarding the effect of LVH (Figure 3). For male patients with hypertension, the AF progression rates differed significantly for those with and without LVH, with LVH being the only independent determinant of AF progression. However, in female patients, the progression rates in patients with and without LVH were similar. So the difference in AF progression seen in the overall group with hypertension is only attributable to the male patients, whereas LVH does not seem to play a role in the progression of AF in female hypertensive patients.

The dissimilar effect of LVH on AF progression in men and women could possibly be explained by the type of LVH. A cardiovascular magnetic resonance imaging study in 741 patients by Rider et al has shown that male patients predominantly show concentric LVH, whereas female patients show both concentric and eccentric LVH.[20] In another study of 64 middle-aged women with at least 10 years of treatment for hypertension, eccentric hypertrophy was more prevalent than concentric hypertrophy on echocardiography (42% vs 5%, $p < 0.001$, mean age 54 years).[21] In a post hoc analysis of the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) trial, concentric LVH was found to be associated with AF recurrences in the rhythm control arm, whereas eccentric LVH was not associated with recurrences.[22] This could be a consequence of diastolic dysfunction in concentric LVH, leading to elevation of filling pressures and left atrial dilatation. It has been shown that concentric LVH has a more profound negative effect on left atrial function and association with LA enlargement compared with eccentric LVH,[23] which could explain the effect seen on AF recurrences in the AFFIRM trial. One could argue that concentric LVH might therefore also be associated with AF progression, explaining the dissimilar effect of LVH on AF progression rates between genders in our population. Unfortunately, we were not able to assess the type of LVH in our population.

For female patients with hypertension, diastolic BP had a protective effect on AF progression. No previous studies have elaborated on this finding. However, Conen et al[24] report a higher incidence of new-onset AF in middle-aged women with a diastolic BP <65 mm Hg and suggest a U-shaped association of diastolic BP and new-onset AF. Unfortunately, no male control group was present in this study.[24] It is possible that a low diastolic BP could also be associated with AF progression, like previously explained. In conclusion, more research is needed regarding gender differences in LVH and the progression of AF.

There are some limitations to the present study. First, we performed a post hoc subgroup analysis of the EHS. Therefore, the data presented in this study should be interpreted with care. This study was conducted in 2003 to 2004, yet the described outcomes are still relevant. Rhythm follow-up was performed in 47% of the included patients and the duration of follow-up was 1 year, limiting the number of AF progression events. In addition, LVH was a dichotomous parameter in the EHS, that is type of LVH was unknown and wall thicknesses were not reported in mm. Furthermore, some patients in the nonhypertensive group used medication like an angiotensin converting enzyme inhibitor, angiotensin receptor blocker, dihydropyridine calcium antagonist or a diuretic. We were not able to assess whether these drugs were prescribed for hypertension or for another indication. Since in these patients hypertension was not checked as concomitant condition at time of conduct of the registry, they were classified as nonhypertensive in the present study. Last, women were underrepresented in this study.

In conclusion, in men with hypertension, LVH is associated with AF progression. This association seems to be absent in hypertensive women.

Disclosures

The investigators have no conflicts of interest to disclose.

Acknowledgment

We are grateful to the EHS team, national coordinators, investigators, and data collection officers for performing the survey. In addition, we are grateful to the sponsors of the EHS on Atrial Fibrillation: main sponsor AstraZeneca, major sponsor Sanofi (formerly known as Sanofi-Aventis), and sponsor Eucomed.

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