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Cardiovascular ultrasound exploration contributes to predict incident atrial fibrillation in arterial hypertension: The Campania Salute Network

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ABSTRACT

Background: Interaction of cardiovascular (CV) risk factors with structural and hemodynamic alterations as combined promoters of atrial fibrillation (AF) is not yet well studied. We designed an observational, longitudinal, retrospective study to predict risk of incident AF by combination of CV risk profile, target organ damage and therapy in hypertensive patients.

Methods and results: We studied 7062 hypertensive patients without history of AF or prevalent CV disease, with ejection fraction (EF) of ≥ 50%, and no more than stage III chronic kidney disease. The patients were selected from an open registry, the Campania-Salute Network, collecting information from general practitioners and community hospitals, in the Campania Region, Southern Italy, networked with the Hypertension Center of Federico II University Hospital in Naples. The end-point of the present analysis was the detection of first episode of AF by ECG or hospital admission, at any point throughout follow-up (median 36 months [IQR = 10–74]). During follow-up, AF developed in 117 patients. Baseline older age, greater left atrial diameter (LAd), left ventricular mass (LVM), and intimal medial thickness (IMT) were independent predictors of AF (all $p < 0.0001$), with no effect of CV risk factors. Beta-blockers and diuretics increased risk of incident AF; use of medications inhibiting renin–angiotensin system (RAS) reduced risk by 50% (all $p < 0.002$).

Conclusions: Older age, increased LAd, and markers of target organ damage (increased LVM and IMT), identify the hypertensive phenotype at highest risk for AF. CV risk factors do not exhibit significant, independent association. Patients on anti-RAS therapy are exposed to lower risk of incident AF.

1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia worldwide [1,2]. The overall incidence of AF increases with age, occurring in 6% of over-65 and up to 15% of over-80 individuals [3,4]. Although many therapeutic strategies are available, AF is still associated with significant cardiovascular (CV) morbidity and mortality [3], including 4 to 5-fold increased risk for stroke, 2-fold higher risk for dementia, 3-fold higher risk for heart failure (HF), and near 2-fold increased risk for overall mortality [4], with consequent rising costs for health care [2].

Among CV risk factors, hypertension is the most prevalent, independent and potentially modifiable condition to reduce incidence of AF [5]. Within the hypertensive population, structural or functional abnormalities of CV system, typical of arterial hypertension, are also reported as markers of increased risk of AF. They include increased arterial stiffness and left atrial (LA) enlargement, left ventricular (LV) hypertrophy, systolic and diastolic dysfunction [6–8]. Recent studies, also suggest that increased carotid intimal medial thickness (IMT), a marker of arteriosclerosis, is associated with increased risk of AF [9]. However, definition of a clear risk profile, by combining clinical, lab and ultrasound examinations of hypertensive patients, in a context of unselected patient population presenting also with comorbidities, is largely incomplete. Specifically, the interaction of CV risk factors with structural and hemodynamic alterations as combined promoters of incident AF is not yet well studied [1], especially in a real-word context. The relatively disappointing results of strategies for primary prevention [5] might be

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at least in part due to the lack of a real-word approach, weighing all possible confounders [10].

Based on the above considerations, we analyzed ultrasound structural and functional characteristics of a large observational registry of treated hypertensive patients, the Campania-Salute Network (CSN), merging with CV risk factors profile and antihypertensive therapy, to generate an integrated model of prediction of incident AF in a real-word context.

2. Methods

2.1. Participants

The CSN is an open registry collecting information from general practitioners and community hospitals in the 5 districts of the Campania Region, in Southern Italy. General practitioners and community hospitals are networked with the Hypertension Center of the Federico II University Hospital in Naples. The database generation of CSN was approved by our institutional ethics committee and signed informed consent was obtained from all participants. All hypertensive patients of the network were referred for baseline echocardiograms and carotid ultrasound to our hypertension center. Detailed characteristics of CSN population have been previously repeatedly reported [11,12]. For the present analysis, we included hypertensive participants without history of AF and CV disease (myocardial infarction, coronary revascularization, stroke, TIA, valvular heart disease), hyperthyroidism, with normal (≥50%) LV ejection fraction, but included patients with obesity, diabetes or chronic kidney disease (CKD) up to stage III. Thus, from the initial population of 11,719 hypertensive patients, 1500 patients were excluded due to the presence of pre-existing CVD or atrial fibrillation, 95 for hyperthyroidism, 61 for abnormal EF, 2362 for absence of follow-up period, 639 because of stage IV or V CKD.

Thus, the study population comprised 7062 hypertensive patients.

2.2. Outcome

Occurrence of the first documented episode of AF (which for convenience will be labeled as "incident AF") was the end-point of the present analysis. Because between the baseline visit at the outpatient clinic and the time of incident AF other CV event or even death could occur, incident composite fatal and non-fatal CV or cerebrovascular events (major CV events) were also recorded to be used as "competing risk event". They included fatal or non fatal acute coronary syndrome, coronary revascularization, fatal or non fatal stroke and transient ischemic attack. All prevalent and incident CV or cerebrovascular events, were adjudicated by the committee for event adjudication in the hypertension center. Adjudication was based on patients' history, contact with the reference general practitioner and clinical records documenting the occurrence of the event/arrhythmia [11,13,14]. AF was adjudicated by the ECG performed at our outpatient clinics or in other hospitals of the network at the time of hospitalization or by the GP at the time of the control visit.

2.3. Measurements and definitions

Diabetes was defined according to 2007 ADA criteria (fasting plasma glucose > 125 mg/dl or anti-diabetic treatment) [15]. Obesity was defined as a BMI ≥ 30 kg/m^2. Systolic and diastolic BPs were measured by standard aneroid sphygmomanometer after 5 min resting in the sitting position, according to current guidelines [16] and after the completion of echocardiograms in supine position. The latter measurements were used to match with echocardiographic measures.

Follow-up BP was evaluated at the last available visit in patients without AF and at visit preceding identification of AF in those with incident AF. As previously reported [17], BP was considered uncontrolled when systolic BP is ≥140 mm Hg or/and diastolic BP is ≥90 mm Hg, under a therapeutic plan that included counseling for lifestyle measures and prescription of at least 2 medications (any class).

2.4. Echocardiography

Echocardiograms recorded in our hypertension center on videotapes, using commercial machines and a standardized protocol, were digitally mastered and read off line by one expert reader under the supervision of a senior faculty member, using dedicated workstations (MediMatic, Genova, Italy).

Measurements were made according to the ASE/EAE recommendations [18]. LA diameter was measured by parasternal short axis view and normalized by the square root of BSA, as suggested by the EchoNoRMAL network study [19]. LV mass was estimated from a necropsy-validated formula and normalized for height in meters to the power of 2.7 (LVMi) [20]. LV hypertrophy (LVH) was defined as LVMi ≥ 50 g/m$^{2.7}$ in men and ≥47 g/m$^{2.7}$ in women [21]. LV diastolic dimension was normalized by height in meters. LV concentric geometry was defined as a relative wall thickness (RWT) ≥0.43 for either gender. LV volumes were estimated from linear measures of LV diameters by the z-derived method [22], and used to compute ejection fraction and stroke volume [23]. The pulsatile component of arterial impedance was estimated as the ratio of pulse pressure to stroke index (PP/SVi), and used as an estimate of arterial stiffness, based on a 2-element Windkessel model [24].

2.5. Carotid ultrasound

Carotid ultrasound was performed with the patients in the supine position and the neck extended in mild rotation. Examinations were recorded on S-VHS videotapes and analyzed as previously described [25]. The maximal arterial intima-media thickness (IMT) was estimated offline in up to 12 arterial walls, including the right and the left, near and far distal common carotid (1 cm), bifurcation, and proximal internal carotid artery, and using an image-processing dedicated workstation (MediMatic, Genova, Italy). Evidence of IMT value higher than 1.5 mm was considered as 'plaque' [25].

2.6. Statistical analysis

Data were analyzed using SPSS (version 21.0; SPSS, Chicago, IL) and expressed as mean ± 1 SD. ANOVA was used to compare baseline characteristics of patients with or without incident AF. The χ^2 distribution was used to compare categorical variables, with the Monte Carlo simulation to obtain exact p values. LVMi and IMT were also dichotomized according to the presence of LV hypertrophy or carotid plaque. To account for therapy, single classes of antihypertensive medications, including anti-renin–angiotensin system (anti-RAS, i.e. ACE inhibitors and/or AT1 receptor antagonists), calcium channel blockers, beta-blockers, and thiazide diuretics, were considered in the analysis according to their overall use during the individual follow-up, based on the frequency of prescriptions during the control visits. Accordingly, all medications used for more than 50% of control visits were considered as covariates in proportional hazards analysis, a method that has been previously used in longitudinal analyses [12,25]. The total number of medications was also measured in each patient.

We calculated hazard ratios (HR) and 95% confidence intervals (CI), by using Cox proportional hazard regression models, entering baseline age, sex, duration of hypertension and duration–age interaction, followed by forward stepwise model building with confounders from exploratory analysis, and finally forcing medications into the model thereafter. Multiple imputation was used to replace missing values. This procedure results in valid statistical inferences that properly reflects the uncertainty due to missing value [26] Incident composite fatal and non fatal CV events preceding AF were considered as a competing risk event in the Cox model [27]. We used this method because the end-point of this analysis, AF, can also be a direct consequence of a preceding CV event directly linked to the possible occurrence of AF, but not censored when using a simple proportional hazard assumption. These events are referred as "competing events", in a sense that they compete with the initial hypothesis to explain the incident event of interest, in our case the development of AF. Thus, we censored acute coronary syndromes occurring before AF, in competition with our end-point that was incident AF. The estimated overall survival of any event is lowered when individuals experience a competing risk event. The null hypothesis was rejected at a two-tailed α-value of ≤0.05.

3. Results

The average age of the study population was 52 ± 12 years. Proportion of women was 43%. Obesity was present in 41% and diabetes in 5% of patients. In the whole study population, LVH was present in 2037 patients (29%) patients and carotid plaque in 2172 (40%); both markers of target organ damage coexisted in 824 patients (12%); in patients developing AF, LVH and carotid plaque, alone or in combination, were

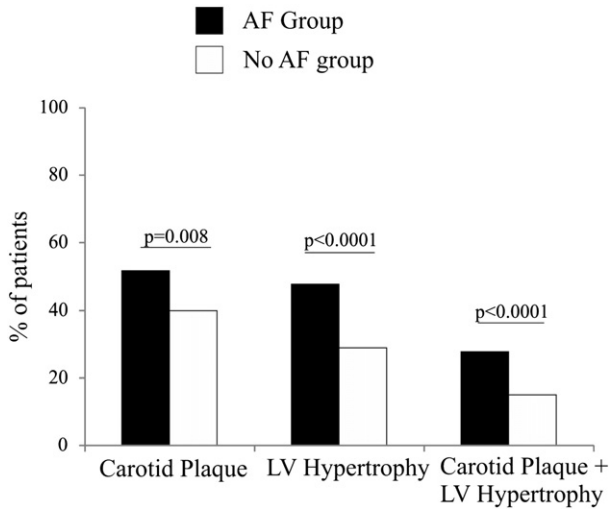

Fig. 1. Prevalence of preclinical cardio-vascular disease at baseline, in patients with incident AF (AF group) and without AF (no AF group). LV = left ventricular.