Factors associated with atrial fibrosis among patients with atrial fibrillation

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FACTORS ASSOCIATED WITH ATRIAL FIBROSIS AMONG PATIENTS WITH ATRIAL FIBRILLATION

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Purpose: This study aimed to use LGE-MRI to characterize age and gender-related differences in left atrial structural changes in patients with atrial fibrillation. We also compared atrial fibrosis of AF patients to a group of non-AF participants.

Dedication: For Elisabeth, Felix, and Tim – Caritas omnipotent

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List of symbols and abbreviations

AF = atrial fibrillation

ANP = atrial natriuretic peptide

AP = action potential

APHRS = Asia Pacific Heart Rhythm Society

AV = atrioventricular node

BMI = body mass index

BNP = brain natriuretic peptide

CAD = coronary artery disease

Cardiac-MRI = cardiac magnetic resonance imaging

CCT = cardiac computed tomography

CHD = coronary heart disease

CT = computed tomography

CVD = cardiovascular diseases

ECG = electrocardiogram

ECM = extracellular matrix

EHRA = European Heart Rhythm Association

Gd = Gadolinium

Gd-Ca = Gadolinium-containing contrast agent

GRAPPA = GeneRalized Autocalibrating Partial Parallel Acquisition

HF = heart failure

HFmrEF = HF with mid-range ejection fraction

HFpEF = HF with preserved ejection fraction

HFrEF= HF with reduced ejection fraction

HIPAA = Health Insurance Portability and Accountability Act

HRS = Heart Rhythm Society

LA = left atrium

LGE-MRI = late gadolinium enhancement magnetic resonance imaging

LV = left ventricle

MI = myocardial infarction

MRT = magnetic resonance tomography

NMR = nuclear magnetic resonance

NOAC = new direct oral anticoagulants

OSA = obstructive sleep apnea

PTCA = percutaneous transluminal coronary angioplasty

PV = pulmonary vein

RMP = resting membrane potential

SD = standard deviation

SOLA= ECE = Society of Electrophysiology and Cardiac Stimulation

SRM = structural remodeling

VKA = Vitamin-K antagonist

Introduction

1.1. Atrial fibrillation, definition, gender-specific aspects, and risk stratification.

Atrial fibrillation (AF), the most severe chronic cardiac arrhythmia, has a significant impact on health and medical care. In the United States alone, between 2.7 million and 6.7 million people have AF, projected to reach 5.6 million to 15.9 million by 2050 (1,2). In the European Union, the prevalence of AF among adults over 55 years of age was estimated at 8.8 million within 2010 and is expected to double by 2060 if age-specific and gender-specific prevalence remain stable (3). It is estimated that there will be 72 million AF patients and 2.9 million AF-associated strokes in Asia by 2050 (4). Beyond North America and Europe, epidemiological evaluation is limited, with a reported prevalence of AF ranging from 0.1% in India and 3% in Israel to 4% in Australia (5,6). The global strain of AF was estimated at 33.5 million in 2010, with almost 5 million new cases reported annually (7). Despite increased awareness and improved AF detection over the last few decades (8), one-third of the total AF population is asymptomatic. A significant proportion of patients with untreated AF can be identified by mass screening (9). As a result, the AF burden worldwide is considerably underestimated.

AF is associated with an increased risk of morbidity, five times higher risk of stroke, three times higher risk of heart failure (HF), two times higher risk of dementia, and 40 percent to 90 percent higher risk of death (10,11). AF-related Medicare spending in the United States is about $16 billion annually (12). The number of AF hospitalizations in Australia tripled between 1993 and 2007, with the rate of increase far exceeding those for HF or myocardial infarction (MI) (13).

In recent years, gender-specific differences in AF have been gaining far less attention than coronary heart disease and stroke. In general terms, "sex" refers to the male-female biological differences, such as genitalia and genetic differences. Gender is harder to define, but it may refer to the male or female role in society, expressed as a gender role, or the definition of an individual's self or gender identity. High body mass index (BMI), hypertension, diabetes mellitus, coronary artery disease (CAD), valvular heart disease, and HF are major risk factors for AF. Still, their prevalence varies between men and women (14-16).

Furthermore, AF is partially heritable (17), and recent studies have suggested differences between men and women in AF genetics (18-20). Studies indicate that women are not only more likely than men to experience AF symptoms (21-23) but also to seek care for these symptoms (21,22). In comparison, AF is associated with worse symptoms and quality of life

(21-23) in women, and an elevated risk of complications like stroke (24) and mortality (25) compared to men. Presently, gender-related inequalities in cardiovascular disease represent a very important field of research. Wide-ranging literature on atherosclerotic mechanisms and their implications date back several decades. Not many physicians, and only some studies, have shown that gender significantly impacts cardiovascular disease pathophysiology and clinical presentation. Until a few years ago, CAD has been widely considered to typically affect the male gender. As a result, most cardiologists have, for a long time, wrongly overlooked that female hearts could experience myocardial ischemia, likewise, the lack of any detectable CAD on coronagraphy was used as a reason to rule out myocardial ischemia in women. Research in the cardiovascular field has diverted attention from the female gender. The lack of appropriate CVD and, subsequently, strategies for managing arrhythmias in women has unfortunately led to an alarming increase in female gender mortality.

The prevention of AF-related strokes is a problem of global public health. AF-related strokes are typical and associated with poor outcome since70-80% of patients die or become disabled (26,27). Proper frequency stratification and early implementation of effective preventive treatment result in a significant decrease for ischemic strokes linked to AF and its mortality (28). Of people with AF, the risk of stroke can be stratified using verified prediction scores such as CHADS2 or CHA2DS2–VASc (29,30). Both available scores use chosen clinical features to rapidly assess stroke risk and provide a rough estimate of the thrombosis risk in a population at a similar risk. The CHADS2 ranking is the most widely used scoring system for stratifying stroke risk in AF (29). In CHADS2, the risk of stroke is measured through a scoring system that grants marks for congestive HF (1 point), hypertension (1 point), age 75 years and above (1 point), diabetes mellitus (1 point), and pre-stroke or transient ischemic attack (2 points). Stroke risk per year decreases according to point score: 1.9% (0 points), 2.8% (1 point), 4.0% (2 points), 5.9% (3 points), 8.5% (4 points), 12.5% (5 points), and 18.2% (6 points) (29). The risk of stroke is classified into three strata based on the CHADS2 cumulative score: low-risk patients with a score of 0, moderate-risk patients with scores of 1–2, and high-risk patients with scores of 3–6 (30). The most recent risk-stratification rating is the CHA2DS2–VASc. This increases risk stratification in patients with CHADS2=0 or 1 and allows truly low-risk patients to be identified. Other points are given for a different age category of 65–74 years (1 point), female sex (1 point), and non-cerebrovascular disease (1 point). Two points will be assigned for 75 years and more of age. Stroke risk increases according to point score per year: 0.5% (0 points), 1.5% (1 point), 2.5% (2 points), 5% (3 points), 6% (4 points), and 7% (5–6 points) (30).

By including additional risk factors, CHA2DS2–VASc helps to identify low-risk patients objectively with a score of 0 who do not need either vitamin-K antagonist (VKA) or new direct oral anticoagulants (NOAC), whereas oral anticoagulation must be addressed for all other patients with CHA2DS2–VASc ≥ 1.

The left atrium is by far the most prominent source for AF. The atria contribute significantly to cardiac function (31,32). In addition to their impact on ventricular filling, they act as a volume reservoir as well as host pacemaker cells and significant parts of the cardiac conduction system [e.g., sinus node, atrioventricular (AV) node]. They secrete natural peptides such as atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) that regulate fluid homeostasis. Many cardiac and non-cardiac problems affect atrial myocardium (33) and are more responsive than ventricular ones (34). The atria are activated by active cardiomyocytes, in addition to the three advanced internodal tracts (35,36), so that any functional or systemic change in the atrial myocardium can cause significant electrophysiological disturbances. However, atrial cells (both cardiomyocytes and non-cardiomyocyte elements such as fibroblasts, endothelial cells, and neurons) respond briskly and extensively to pathological stimuli. They are sensitive to several genetic influences (33). Responses include atrial cardiomyocyte hypertrophy and contractile dysfunction, arrhythmogenic changes in cardiomyocyte ion-channel and transporter activity, proliferation of atrial fibroblasts, hyperinnervation, and thrombogenic modifications (32). Fibrosis also increases the number of fibroblasts and changes their properties, thereby supporting AF by modifying the electrophysiological activity of cardiomyocytes coupled to fibroblasts by cardiomyocyte-fibroblast interactions (37). Another way fibroblast may promote arrhythmogenesis is by generating large amounts of extracellular matrix (ECM) proteins, especially collagen, which modify the architecture of cardiomyocytes and disrupt electrical continuity. In AF, tissue fibrosis occurs parallel to local conduction disruptions and rises in AF persistence, both during the production and resolution of experimental cardiac HF, instead of a number of other cardiac HF-related changes (38, 39). ECM alterations in fibrotic tissue could lead to conduction abnormalities and the promotion of AF in many ways. Loss of side-to-side cardiomyocyte connections due to insulating collagen in cardiomyocyte bundles have been proposed to generate zigzag conduction patterns and facilitate atrial micro re-entry with ageing (40). Fibrosis occurs around cardiomyocyte bundles. Longitudinal conduction is uninterrupted and could even be accelerated due to better insulation of cable-like bundles. The effect of reparative fibrosis, in which dead cardiomyocytes are replaced by fibrous tissue, physically

separates cardiomyocytes in the longitudinal direction and interferes with longitudinal conduction (41).

Hence, atrial pathology has a significant impact on cardiac output, the frequency of arrhythmia, and the risk of strokes (31,42). Recently, the Consensus Community on Atrial Cardiomyopathies of EHRA (European Heart Rhythm Association) / HRS (Heart Rhythm Society) / APHRS (Asia Pacific Heart Rhythm Society) / SOLAECE (Society of Electrophysiology and Cardiac Stimulation) described such atrial pathologies as any set of structural, architectural, contractile or electrophysiological changes affecting the atria with the potential for clinically relevant manifestations (43). Fibroblast coupling to cardiomyocytes can cause several changes in the properties of the action potential (AP), including changes in the pace-making role. Fibroblasts are electrically coupled to cardiomyocytes (44). Fibroblasts modulate cardiomyocyte electrical activity by depolarizing or hyperpolarizing cardiomyocytes, depending on the relative values of cardiomyocyte vs. fibroblast transmembrane potential. Lacking active phase 0 depolarization, fibroblast cell membranes possess a capacitance parallel to their resistance, making them "leaky capacitors". They also display a variety of ion channels that show voltage- and time-dependent conductance (45). When cardiomyocytes are depolarized to voltages positive to about −30 mV (the standard fibroblast resting potential), the gap-junctional flow of positive ions towards the more negatively charged fibroblast produces repolarizing cardiomyocyte current flow that can mimic transient outward current. As a result, cardiomyocyte–fibroblast coupling depolarizes cardiomyocyte resting membrane potential (RMP), slows conduction by drawing off excitatory current flow during phase 0, and can increase or decrease AP duration depending on fibroblast resting potential and cardiomyocyte–fibroblast coupling properties (46). In pathological conditions, intervening fibroblasts can couple otherwise-uncoupled cardiomyocytes, producing prolonged conduction that can significantly promote reentry (47).

1.2. The magnetic resonance tomography and its role in the diagnosis and prognosis of cardiac diseases and AF.

1.2.1 Definition.

The magnetic resonance tomography abbreviated MRT or MR is an imaging technique used primarily of medical diagnostics to represent the structure and function of the body tissues and organs. It is technically based on the principles of nuclear magnetic resonance (NMR),

particularly field gradient NMR, and is sometimes referred to as nuclear spin tomography (colloquially shortened sometimes to nuclear spin).

The sectional images of the human (or animal) body can be visualized with the MRI, allowing for inspection of the organs and detection of pathological changes. There are no dangerous X-rays or other ionizing radiation produced or used in the system, though the effects on living tissue from the alternating magnetic fields are not fully understood (48).

1.2.2. MRI physical basics.

The procedure is based on the fact that, by a mixture of static and high-frequency magnetic fields, the atomic nuclei in the studied tissue are selectively excited synchronously to a specific movement, producing a detectable signal form of an alternating voltage until the movement has subsided. This action is called "Larmor precession" and is physically similar to a robot gyroscope to detect if its rotational axis is not vertical by conducting a precession around the vertical. A resonance condition is to be met for both the excitation and the identification of the signal; in this manner it is possible to determine the position of the processing nuclei by means of inhomogeneous static magnetic fields. Those atomic nuclei in the tissue molecules analyzed (such as the hydrogen nuclei) have an intrinsic angular momentum (i.e., nuclear spin) and are therefore magnetic. Upon applying a strong static magnetic field, these nuclei create a minor longitudinal magnetization in the static field orientation (i.e., Paramagnetism). Because of a short-term high-frequency alternating field applied in the radio frequency spectrum, this magnetization can be deflected (i.e., tilted) from the static field's direction, signifying partial or complete transformation (i.e., saturation) into a transverse magnetization phase. Transverse magnetization appears to process directly around the field direction of the permanent magnetic field, noting though that the magnetization direction rotates. This tissue magnetization precession action, such as the magnet's dynamo rotation in a coil (i.e., receiver circuit), produces an electrical voltage and can be observed. The amplitude is proportional to the magnetization of the transverse. The transverse magnetization decreases (again) after switching off the alternating high-frequency field, so the spins align themselves parallel to the static magnetic field. They need a signature cool-down for that relaxation. This relies on the chemical compound in which the processing hydrogen nucleus is found and the molecular condition. The different types of tissue thus distinguish characteristically in their signal, resulting in different signal strengths (i.e., Brightnesses) in the resulting image (48).

1.2.3 Principle of image evaluation in the MRI.

Since it depends on various parameters (such as the magnetic field intensity), there are no standard values for the signal of specific tissues, as well as no specified unit comparable in computed tomography to the Hounsfield units. The MR console displays only subjective (i.e., Arbitrary) units that are not directly eligible for diagnosis. Instead, the picture's description is based on the average contrast, the related weighting of the measurement sequence (i.e., Synonymous weighting) and the signal differences between known and unknown tissues. Therefore, in the study, the definition of a lesion is not about "color" or "black," but delineated as hyperintense for high-signal, white and hypointense for low-signal, dark.

Depending on the weighting, the various tissues are expressed in a typical strength distribution:

- Hyperintense (i.e., high in signal, light) and fatty/rich tissues (e.g., bone marrow) occur in T1 weighting. T1 weighting is a pulse sequence in MR imaging and depicts differences in the signal based upon intrinsic T1 relaxation time of various tissues. Thus, this weighting is well-suited for the anatomical description of organ systems and, particularly, for the administration of contrast agents (e.g., gadolinium) to help delimit uncertain structures (e.g., tumor).
- Stationary fluids appear hyperintense in the T2 weighting. T2 weighting is a pulse sequence highlighting differences in the T2 relaxation time of tissues, so that liquid-filled structures appear rich in signal (i.e., bright). As a result, this weighting is suitable for presenting effusions and edema, as well as distinguishing cysts from solid tumors, for example. In contrast, X-ray images, particularly in the special computed tomography (CT) X-ray technique, the terms *hyperdense* and *hypodense* describe the relative degree of blackening.
- Proton-weighted (PD) images are bright but sluggish. Cartilage, for example, can be examined in great detail. Therefore, PD images, in combination with a fat saturation pulse, are common in joint studies.
- MR images are evaluated algorithmically in voxel-based morphometry in order to determine objective parameters and test them statistically. Specifically, these methods are used when studying the human brain to assess the size of specific brain structures.

1.2.4. Advantages of the MRI.

The advantage of utilizing MRI over other imaging techniques is the superior contrast between soft tissues. This contrast is the direct result of different types of tissue varying in fat and water content, with the distinct benefit of a process that involves no harmful ionizing radiation. The latest, faster imaging techniques allow for individual slices to be scanned in fractions of a second, offering true real-time MRI that replaces previous traditional fluoroscopic-based attempts. This facilitates the ability to visualize organ movements, and even observation of a medical devices' location during an intervention (i.e., interventional radiology). So far, individual slices paired with an electrocardiogram (ECG) are used to capture the beating heart, which integrates data from multiple cardiac processes into complete images. In comparison, newer real-time MRI methods offer direct cardiac imaging without ECG synchronization and free breathing with a temporary resolution of up to 20 ms. The lack of radiation exposure is also essential, which is the favorable validation why this approach is used in baby/child research and during pregnancy instead of CT (48).

1.2.5. Cardiac magnetic resonance imaging (cardiac MRI).

Cardiac MRI is an increasingly important screening technique. The technique allows excellent anatomical visualization of cardiac and extracardiac systems, projections of cardiovascular function, and classification of functional tissue (using "mapping" techniques).

Specifically, there are indications for use of cardiac MRI in the following diseases:

- Congenital heart defects
- CAD
- Non-ischemic cardiomyopathies
- Infectious myocardial diseases (peri-/myocarditis)
- Cardiac tumors
- Coronary blood clots (thrombi)
- Valvular heart disorder
- Large vessel thorax diseases

The Late Gadolinium Enhancement (LGE) method for evaluating myocardial infarction has become a standard clinical technique in cardiac MRI over the last decade.

The most commonly used contrast agent for MR is the chelated form of water-soluble gadolinium (Gd). It primarily accumulates in the intravascular space and permeates the interstitial space, except for the brain (due to the blood-brain barrier). The Gd contrast agent(Gd-Ca) undergoes contact between the interstitial and intravascular space and does not enter the intracellular space. Following intravenous injection of Gd, due to various kinetic properties, both normal and abnormal myocardium will exhibit different Gd concentration curves. Compared to normal myocardium, the lack of intact cardiomyocytes causes abnormal myocardium, such as infarcted or scarred myocardium, to have more significant interstitial space. The abnormal myocardium cultivates more contrast agent than the healthy myocardium, with a time delay of ~10 minutes after Gd injection. As the Gd-chelate is a contrast agent that primarily shortens the longitudinal relaxation time (T1) of the proton spins, irregular myocardium with enhanced Gd concentration will display higher signal (i.e., hyperenhancement) on LGE-MRI images. The LGE-MRI is performed using a T1-weighted rapid GRE series combined with a pre-pulse inversion-recovery to null the standard myocardial signals. This sequence's images display a strong contrast between normal myocardium (i.e., dark or no signal) and abnormal myocardium (i.e., bright or hyperenhancement). The sequence relies on operators to select between various inversion times (TIs) that best suppress the signal from the normal myocardium (~250 ms) for suitable TI. In practice, TI varies with the time following Gd injection, so operators may need to change TI multiple times during LGE-MRI acquisition, consequently extending the time of the scan. A new sequence of LGE-MRIs called phase-sensitive IR (PSIR) has recently been established to resolve this problem. The PSIR series is designed to reliably nullify the normal myocardium across a period of TIs. Operators can only use a default TI for the entire LGE-MRI acquisition without having to change it. A single slice of 2D LGE-MRI is commonly acquired in one breath-hold. Similarly, for parallel imaging, multiple slices can generally be obtained in one breath-hold. When patients cannot hold their breath, 3D LGE-MRI with respiratory navigator technique can be done in about 5 minutes to comprise the entire heart cycle.

1.2.6. LGE-MRI and the evaluation of the atrial fibrosis.

The Gd-Ca diffuses rapidly from capillaries after intravenous administration due to contrast kinetics. These properties inhibit the ability to enter into cells with intact membranes and thus accumulates in the extracellular space. Likewise, this leads to an accumulation of contrast in the areas of fibrosis. As a result, in T1-weighted MRI scans, fibrotic tissue has higher signal strength than a healthy myocardium. For LGE-MRI, the image contrast between fibrotic and

normal tissues is enhanced by inversion or saturation of radiofrequency pulses using magnetization preparation (49). Research using LGE-MRI to detect structural changes in atrial tissue has made an essential contribution to the understanding of pathophysiology and AF progression. Moreover, atrial fibrosis imaging using MRI has grown to be a method to enhance the clinical outcome of AF ablation procedures by allowing for a patient-specific, individualized approach to treatment. It has been shown that LGE-MRI predicts the AF ablation outcome based on the degree of atrial fibrosis from pre-procedural imaging. Also, a greater understanding of the underlying mechanisms of atrial structural remodeling is essential in minimizing the incidence of AF-associated complications (e.g., ischemic stroke and heart failure) (49).

2.1. Aim and hypotheses

The research aimed to use LGE-MRI to identify age-and gender-related differences in left atrial structural changes in AF patients. We have compared the AF patients' atrial fibrosis to a small group of outwardly healthy individuals without history, signs or symptoms of AF. The thesishas two hypotheses. Hypothesis one is that female AFpatients of advanced age are associated with a higher atrial fibrosis burden. Hypothesis two is that clinical thromboembolic risk does not necessarily equate with the severity of atrial fibrosis.

2.1.1. Materials and methods

2.1.1.1. Study sample

This research involved 939 consecutive patients at the University of Utah who were presenting for AF treatment between 2006 and 2013. Patient profiles and related medical history and comorbidities were collected and subsequently tabulated, de-identified, and coded for review. The AF-type was classified as paroxysmal, persistent, or permanent AF as defined in the ACC / AHA / ESC Guidelines (53) upon entry into the database. In all patients, LGE-MRI was obtained upon acceptance of catheter ablation as treatment strategy for their arrhythmia. Thiscohort did not contain patients with previous left atrial ablation. Thirty-one AF patients were excluded due to low image quality of the MRI,due toan inability to measure atrial fibrosis, resultingin the final analysis cohort of 908 patients (Figure 1). There were no significant variations in baseline characteristics between the 31 patients excluded and the final cohortfor final analysis.

Fifteen control participants were recruited in age- and sex-matched fashion to the AF cohort. Control patients were recruited through flyers posted in the waiting room of the University of

Utah endoscopy center; aimed at subjects presenting for screening colonoscopies who belong to the same age group of most AF patients. Inclusion criteria for control subjects were willingness to undergo a contrast MRI of the heart. In contrast, exclusion criteria included known AF, coronary artery disease, congestive heart failure, or valvular heart disease; as well as, contraindications to MRI scanning, including severe obesity exceeding the scanner weight limit, poor kidney function (estimated glomerular filtration rate <30), or known allergy to gadolinium contrast. The database and control subject recruitment protocols were approved by the institutional review board and were HIPAA (Health Insurance Portability and Accountability Act) compliant.

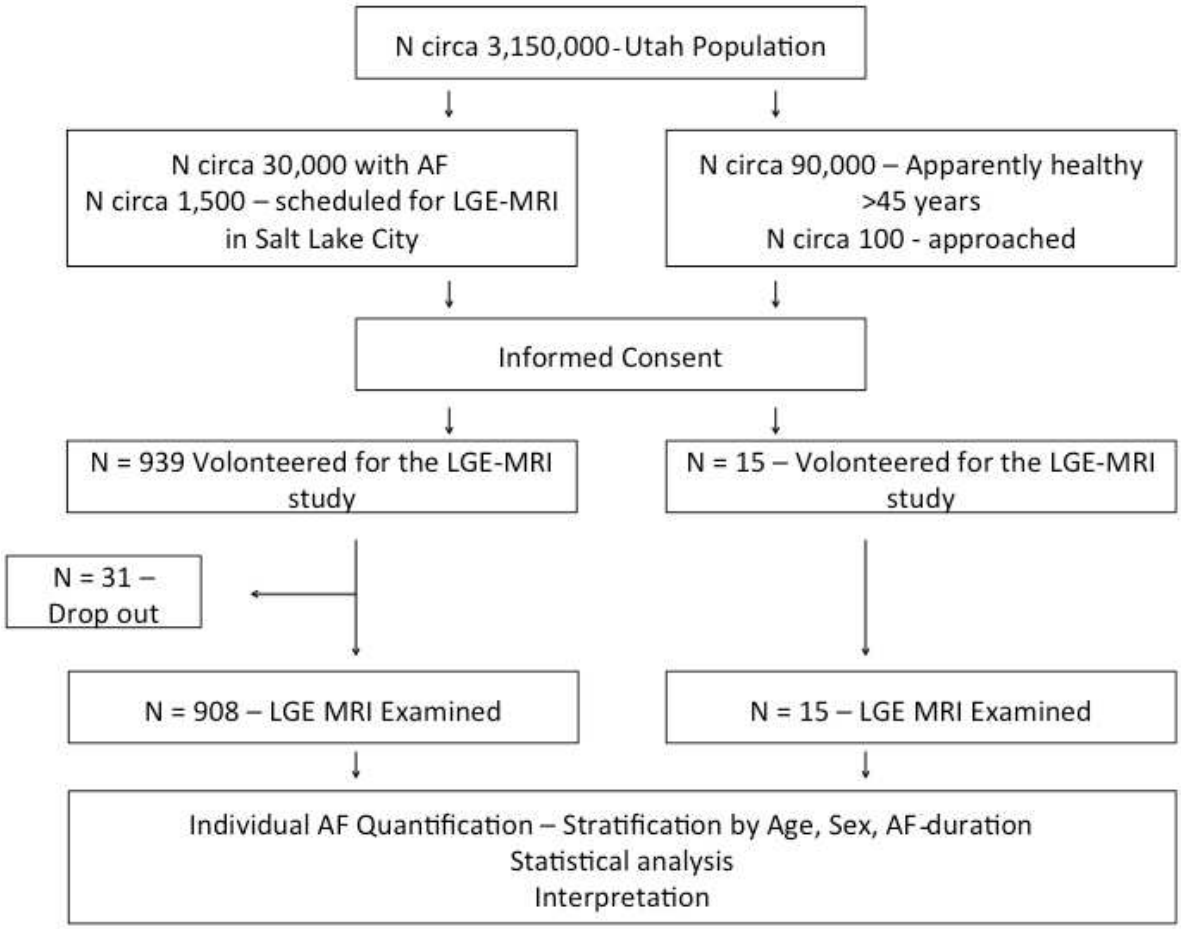


Figure 1. Study flow-chart.

In the current study, LGE-MRI exams were performed on a 3T Verio clinical MRI (Siemens Medical Solutions, Erlangen, Germany) using an array receiver coil. The scan was acquired 15min following contrast agent injection [0.1mmol/kg, Mulithance (Bracco Diagnostic Inc., Princeton, NJ, USA)] using a three-dimensional inversion recovery, respiration navigated, electrocardiogram (ECG)-gated, gradient echo pulse sequence. Typical acquisition parameters were: free-breathing using navigator gating, a transverse imaging volume with voxel size= 1.25x1.25x2.5mm (reconstructed to 0.625x0.625x1.25mm), Repetition time (TR)/Echo time (TE)= 5.4/2.3ms, inversion time (TI)= 270-310ms, GeneRalizedAutocalibrating Partial Parallel Acquisition (multi-coil parallel imaging techniques, GRAPPA) with R = 2 and 46 reference lines. ECG-gating was used to acquire a small subset of phase encoding views during the diastolic phase of the left atrium (LA) cardiac cycle. The time interval between the R-peak of the ECG and the start of data acquisition was defined using the LA's cine images. Fat saturation was used to suppress the fat signal. The TE of the scan (2.3ms) was chosen such that fat and water are out of phase, and the signal intensity of partial volume fat-tissue voxels was reduced, allowing improved delineation of the LA wall boundary. The TI value for the LGE-MRI scan was identified using a scout scan. The typical scan time for the LGE-MRI study was 5–10 min depending on subject respiration and heart rate (51).

2.1.1.2. Quantification of left atrial fibrosis

LA wall volumes were manually segmented by three trained observers from the LGE-MRI images using the Corview image processing software (MARREK Inc., Salt Lake City, UT)(52). First, the LA's endocardial border was defined, including the extent of pulmonary vein (PV) sleeves, by manually tracing the LA-PV blood pool in each slice of the LGE-MRI volume. Next, the endocardial segmentation was morphologically dilated and then manually adjusted to assess the boundary of the epicardial LA surface. Finally, the endocardial segmentation was subtracted from the epicardial segmentation to define a wall segmentation, manually edited to exclude the mitral valve and PVs. Thus, the resulting LA wall segmentation included the 3D extent of both the LA wall and the PVs' antral regions (Figure 2). After segmentation of the LA wall, we estimate an intensity threshold for enhancement (i.e., fibrosis) by inspection with an interactive intensity threshold tool within Corview. The thresholding tool displays the mean and standard deviations of the MRI voxel values in the LA wall on top of a histogram of the wall intensity values. The user then selects a threshold value for enhancement using a slider. As the threshold slider is moved, the user can see which pixels are being set in both a 2D display of the MRI image stack and a 3D volume rendering of the MRI. Typically, enhancement values

are found to be in the range of 2–4 standard deviations from the mean value. Once the threshold has been determined, the percentage of enhancement is calculated as the number of voxels in the LA wall segmentation with values above the threshold divided by the total number of voxels in the LA wall segmentation. The study patients were then assigned to one of four structural remodeling (SRM) categories based on LA wall enhancement as a percentage of the total LA wall volume, with stage I defined as <10%, stage II ≥10–20%, stage III ≥20–30%, and stage IV ≥30%. Based on the SRM, patients were classified in 4 groups: Utah I (≤5% LA wall enhancement), Utah II (>5% to≤20%), Utah III (>20% to ≤35%), or Utah IV (>35%)(52).

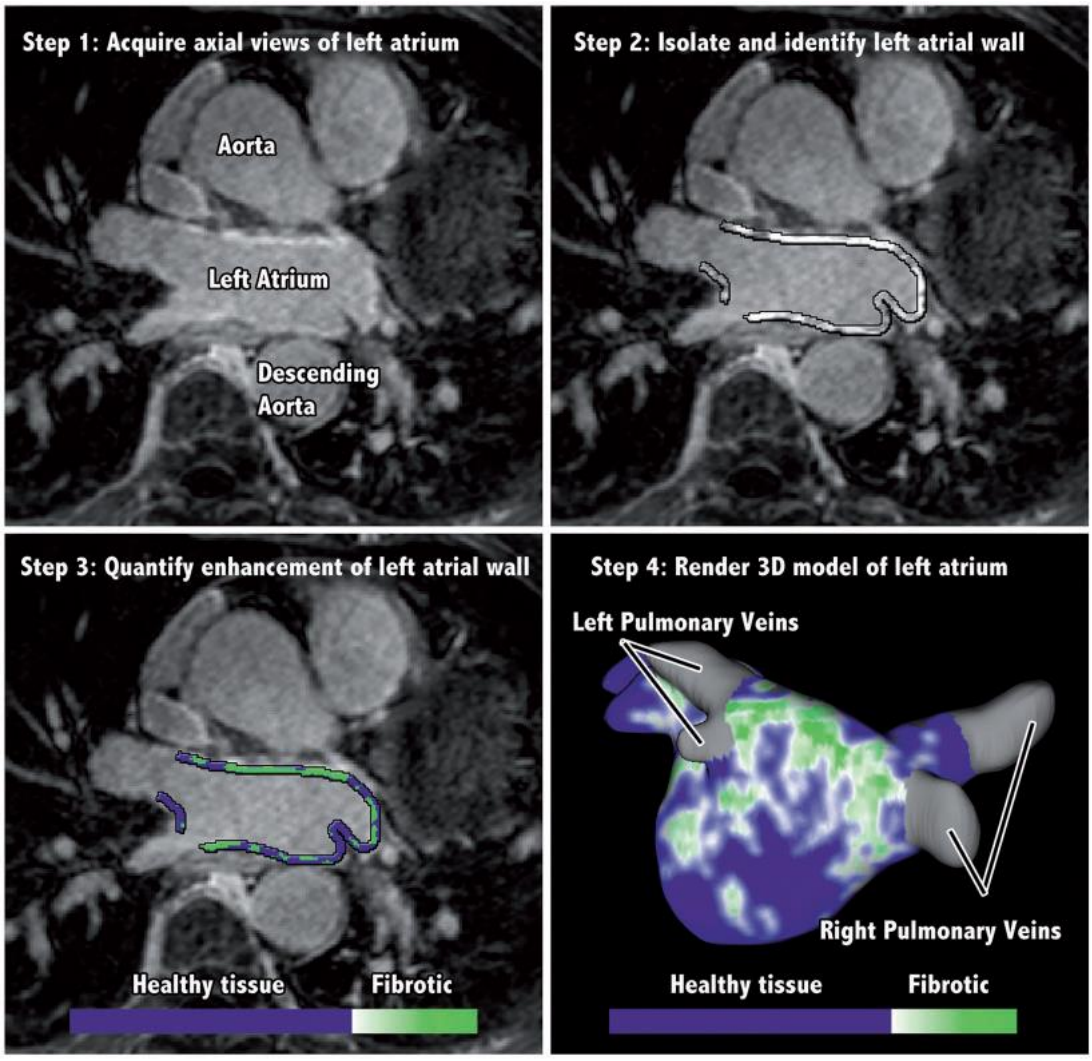


Figure 2. Late-gadolinium enhancement magnetic resonance imaging quantification of atrial fibrosis. The atrial wall is segmented, and hyper-enhancing diseased tissue (i.e. fibrosis) is identified (left). Three-dimensional reconstruction of the left atrium (LA) shows the overall extent and distribution of fibrosis (right).

2.1.1.3. Statistical analysis

Statistical analysis was performed using STATA 12 (StataCorp, College Station, TX, USA). Normal continuous variables are presented as mean ± standard deviations. A two-tailed Student's t-test was used to test for statistical significance for continuous variables. Categorical variables are presented as numbers and percentages of the total. Pearson's χ^2 or Fisher's exact test was used to assess statistical significance. Linear regression analysis was used to study univariate and multivariate statistical associations between fibrosis and other clinical variables and 95% confidence intervals were added. P-values of less than 0.05 were considered statistically significant. For comparison of CHA2DS2-VASc score and left atrial fibrosis, patient data were saved in a dedicated database. The linear regression analysis was performed using IBM-SPSS version 23.

2.2. Results

2.2.1 Baseline characteristic.

Among the AF patients, 316 were female (34.8%), and 592 (65.2%) were male (Table 1). Men had a higher prevalence of CAD (26.6% vs. 12.0%; χ^2= 5.572 /df 1/ P< 0.001) and OSA (26.0% vs. 15.9%; %; χ^2= 2.57 /df 1/ P< 0.001) compared to women. Women in our cohort, on the other hand, had a higher prevalence of mitral valve regurgitation (10.2% vs. 5.2%; %; χ^2= 2.024 /df 1/ P = 0.003). There were no significant differences between the two sex groups regarding the history of smoking, hypertension, diabetes, or congestive heart failure in this cohort.

In the control group, 5 patients (33.3%, mean age 59± 10, range 38-70 years) were female, and 10 (66.7%, mean age 50± 20 years, range 22-78) were male. The overall age was 65± 7 years. There were no comorbidities reported. The LV ejection fraction was normal in all participants, and no other echocardiographic aberrations were reported.

Table 1. Baseline characteristics of the patients with atrial fibrillation and control group

Variable	**Overall AF n = 908**	**Male AF n = 592**	**Female AF n = 316**	**P-value***	**Control group, overall n = 15**	**Male n = 10**	**Female n = 5**
Age (years)	66.2±11.8	64.9±11.7	68.71±11.6	<0.001	65± 7	50± 20	59± 10
Diabetes (%)	17,3	16	19,6	0.180	0	0	0
Hypertension (%)	64.2	64.3	64	0.925	0	0	0
Coronary artery disease (%)	21.4	26.6	12	<0.001	0	0	0
Congestive heart failure (%)	12.6	11.9	14	0.37	0	0	0
>1+ mitral regurgitation	7.2	5.2	10.7	0.003	0	0	0
Prior stroke (%)	10.6	7.2	16.7	<0.001	0	0	0
Smoking history (%)	25.5	27.5	21.9	0.0759	0	0	0
Obstructive sleep apnea (%)	22.4	26	15.9	<0.001	0	0	0
Body mass index (kg/m^2)	29.9±6.8	30.3±6.3	29.1±7.8	0.022	28.8±1.8	29.1±2.1	28.1±0.5
Paroxysmal AF (%)	41.2	37.3	42.8	0.161	0	0	0
Persistent AF (%)	54.7	55.4	50.63	0.169	0	0	0
Permanent AF (%)	4.1	7.27	7.26	0.993	0	0	0
Median time from AF diagnosis (months)	24	24	21.5	<0.001	0	0	0
Prior anti-arrhythmic drug therapy (%)	17.5	18.8	15.1	0.380	0	0	0

*Comparison between male and female AF patients (unpaired t-test)

2.2.2. Arrhythmia history and phenotype.

There was no statistically significant difference in the clinical phenotype of AF between the two sex groups: paroxysmal AF 42.08% in women vs. 37.33% in men; χ^2= 1.96 /df1/ P = 0.161; persistent AF 50.63% in women vs. 55.4% in men; χ^2= 1.88 /df1/ P =0.169; permanent AF 7.27% in women vs. 7.26% in men; χ^2= 0.001 /df1/ P = 0.993.

2.2.3 Left atrial volume and fibrosis.

Left atrial fibrosis was detectable in all patients. Figure 3 demonstrates the different stages of left atrial structural remodeling. Female AF patients had higher atrial fibrosis compared to male AF patients (17.5± 10.1 vs. 15.3± 8.9; %; χ^2= 1046.53 /df 1/ P<0.001). Left atrial volume was lower in women than in men (91.4± 37.4 ml vs. 111.3± 43.7 ml; %; χ^2= 79261 /df 1/ P<0.001). Indexed to body surface area, the difference in LA volume dissipated: 50.5± 19.8ml/m^2 in women vs. 52.6± 22.1 ml/m^2 in men; %; χ^2= 797.32 /df 1/ P=0.186.

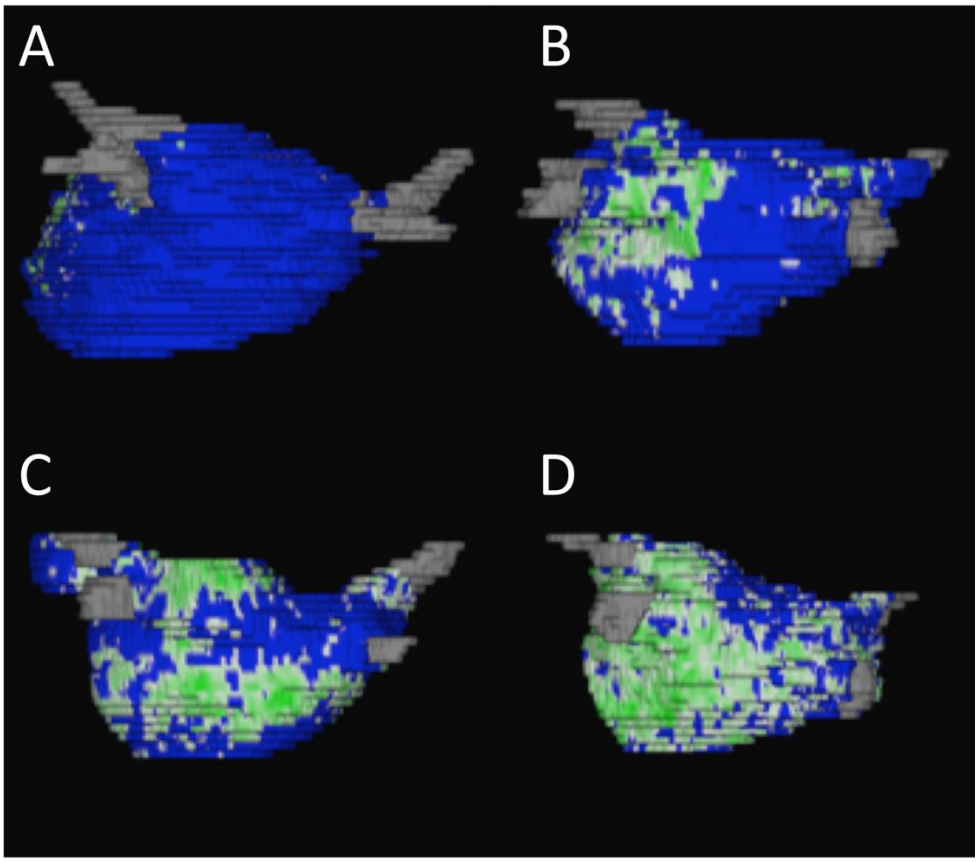


Figure 3. Different stages of left atrial structural remodeling. A =Utah I (≤5% LA wall enhancement), B = Utah II (>5% to≤20%), C = Utah III (>20% to ≤35%), or D = Utah IV (>35%). Blue = healthy myocardium, green = fibrotic tissue, pulmonary veins = gray.

2.2.4. Age and sex differences in atrial fibrosis.

The AF cohort's mean age was 66± 12 years (median 67; range 24–92 years). On the initial presentation to the AF clinic, women had a higher mean age than men (68.7± 11.6 vs. 64.9± 11.7 years; P<0.001). Patients were grouped by the decade of life. There were eight patients younger than 30 years**,** 20 patients 30–39 years, and 5 patients older than 90 years. Patients younger than 40 years were lumped together in one group for analysis purposes, as were patients older than 80 years in another group. The relationship between age and fibrosis showed a linear trend, with higher fibrosis levels with advancing age (Figure 4).

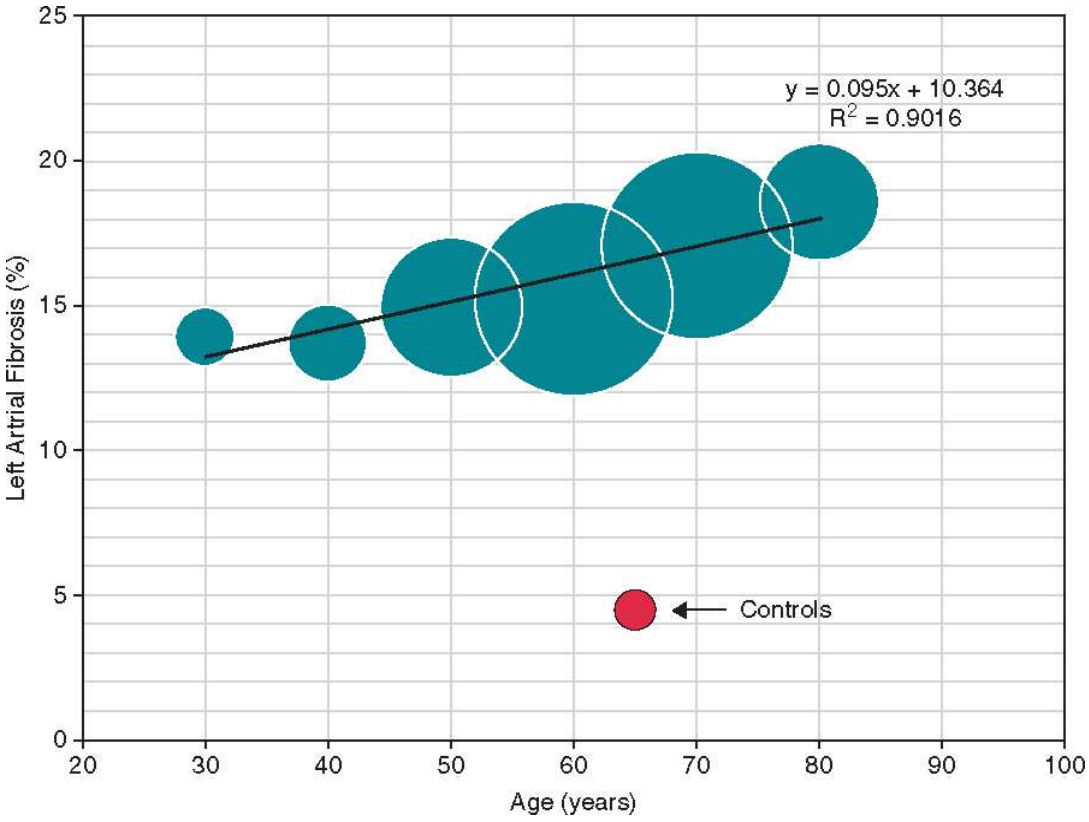


Figure 4. Correlation between age and left atrial fibrosis.

Atrial fibrosis was higher in women than men across all age groups, with the exception of the older than 80 years group (Figure 5). This was statistically significant in the 50-59 age group (N = 152, P = 0.007, 95% CI, 13.72%-16.2%) and age group 70-79 (N= 274, P = 0.006, 95% CI, 15.91%-15.9%-18.2%).

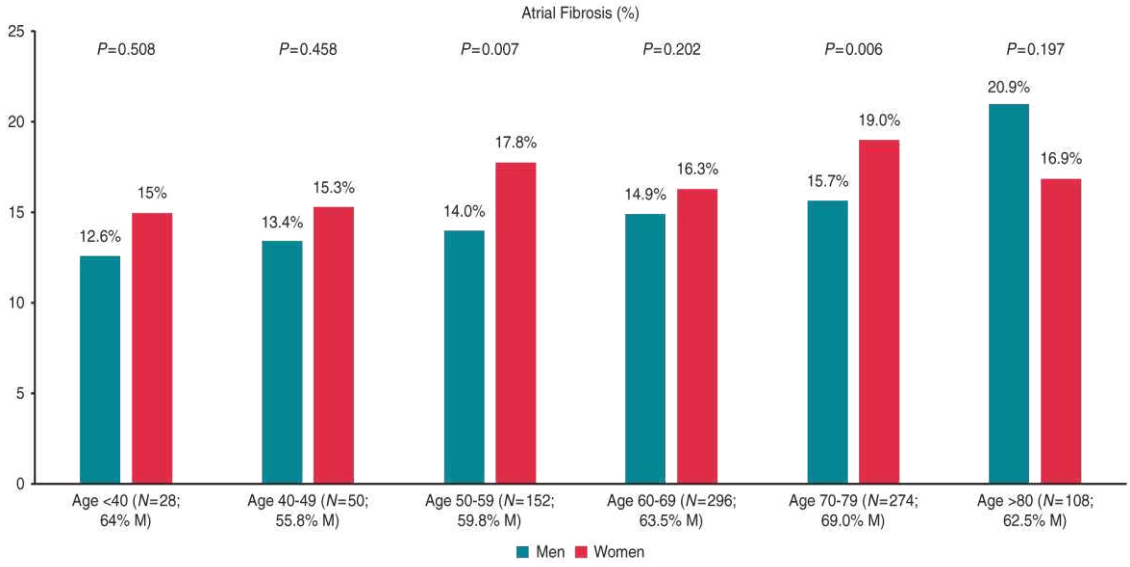


Figure 5. Atrial fibrosis in different age groups - comparison between men and women.

2.2.5. CHADS2, CHA2DS2-VASc, and stroke.

In AF patients, the CHADS2 score was higher in women than in men: 1.64± 1.33 vs. 1.27± 1.09; %; χ^2= 26.557 /df 1/ P<0.001. There were more men with CHADS2 of 0 or 1 than women (64.16% of men in the cohort vs. 35.84% of women in the cohort). With the CHA2DS2-VASc score, which incorporates sex category into the calculation, the difference between women and men was even more pronounced: mean CHA2DS2-VASc score was 3.14± 1.44 for women vs. 1.91± 1.37 for men; χ^2= 291.902 /df 1/ P<0.001 (2.15± 1.44 vs. 1.91± 1.37; P =0.0213). A total of 89 patients presented with a history of stroke or transient ischemic attack (TIA). More women had a history of stroke or TIA compared with men: 50 (15.82%) vs. 39 (6.59%);χ^2= 1.74 /df 1/ P<0.001 (Figure 6). Women with a prior history of stroke or TIA had significantly higher level of atrial fibrosis than women without this history (20.7± 13.0% vs. 16.9± 9.4%; 95%CI 16.4%-18.6%, P=0.016). No such difference in atrial fibrosis was seen in men, either with or without a history of stroke or TIA (15.3 ± 9.0 vs. 15.2 ± 8.1; 95% CI 14.5%-15.98%, P=0.939). CHA2DS2-VASc was significantly higher in patients with former stroke than those without former cerebral event (4.36 ± 1.22 vs. 2.08 ± 1.3; %95 CI 2.25%-2.45%, P<0.001).

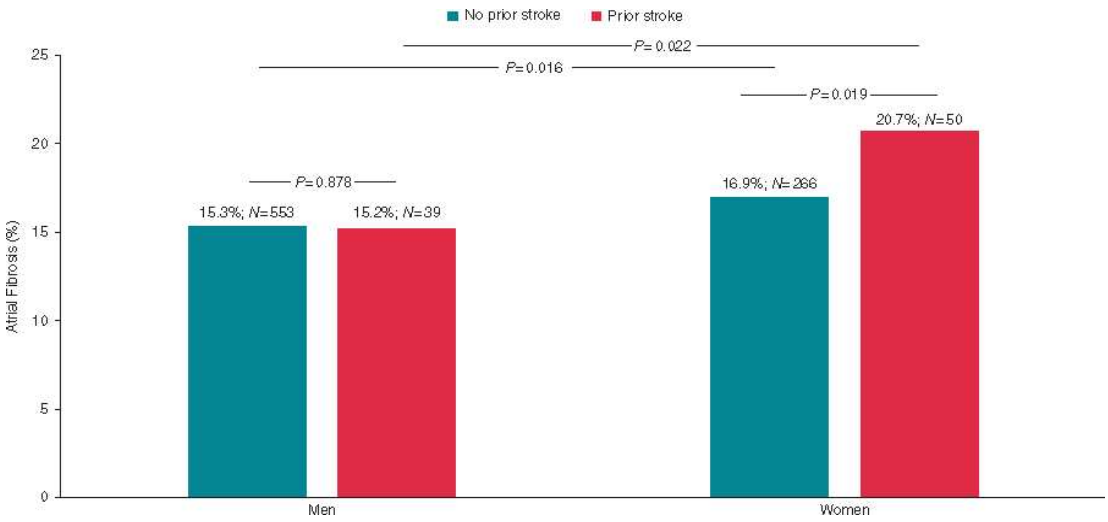


Figure 6. Extent of atrial fibrosis by sex, according to history of stroke.

2.2.6. CHA2DS2-VASc and left atrial fibrosis

The degree of left atrial fibrosis ranged from 1.4% to 80.2% in the whole cohort. The CHA2DS2-VASc Score ranged from 0 to 8 in all patients. The contribution of patients in different CHA2DS2-VASc groups was 9.57% of the patients with 0 points, 23.56% of the patients with 1 point, 22.85% of the patients with 2 points, 22.13% of the patients with 3 points, 13.04% of the patients with 4 points, 6.46% of the patients with 5 points, 1.56% of the patients with 6 points, 0.6% of the patients with 7 points and 0.23% of the patients with 8 points. Left atrial tissue changes detected using LGE-MRI were found in all CHA2DS2-VASc groups with widespread fibrosis. The average left atrial fibrosis was 14.21% ± 7.7% with a range from 1.98% to 36.89% in patients with CHA2DS2-VASc 0, 14.14% ± 7.3% with a range from 1.4% to 43.35%; in patients with CHA2DS2-VASc 1, 16.43% ± 10.18% with a range from 2.58% to 62.7%; in patients with CHA2DS2-VASc 2, 16.44% ± 10.25% with a range from 1.62% to 80.2%; in patients with CHA2DS2-VASc 3, 18.61% ± 9.7% with a range from 4.75% to 50.18%; in patients with CHA2DS2-VASc 4, 17.98% ± 11.76% with a range from 2.14% to 55% in patients with CHA2DS2-VASc group 5, 23.47% ± 13.6% with a range from 3.91% to 50.7% in patients with CHA2DS2-VASc 6, 14.86% ± 2.4% with a range from 13.72% to 18.99%; in patients with CHA2DS2-VASc 7 and 21.25% ± 4.5% with a range from 18.05% to 24.45%; in patients with CHA2DS2-VASc 8 (Figure 7).

Despite a significant difference in the risk of stroke, the patients with CHA2DS2-VASc of 1,2 vs. 7 have had a similar extent of atrial fibrosis.

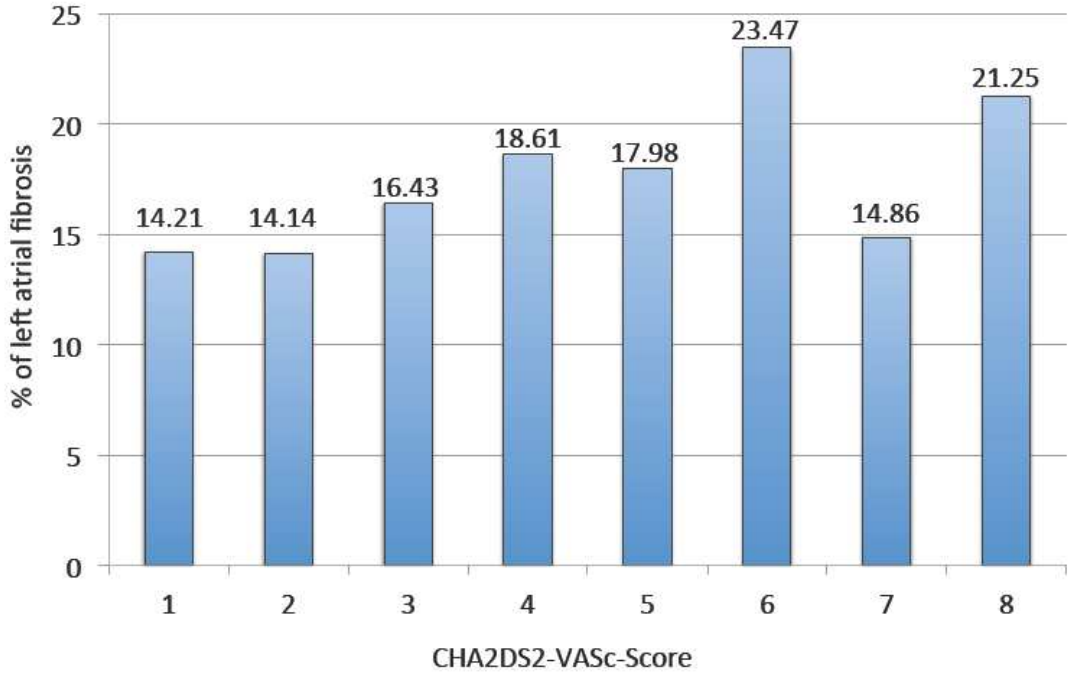
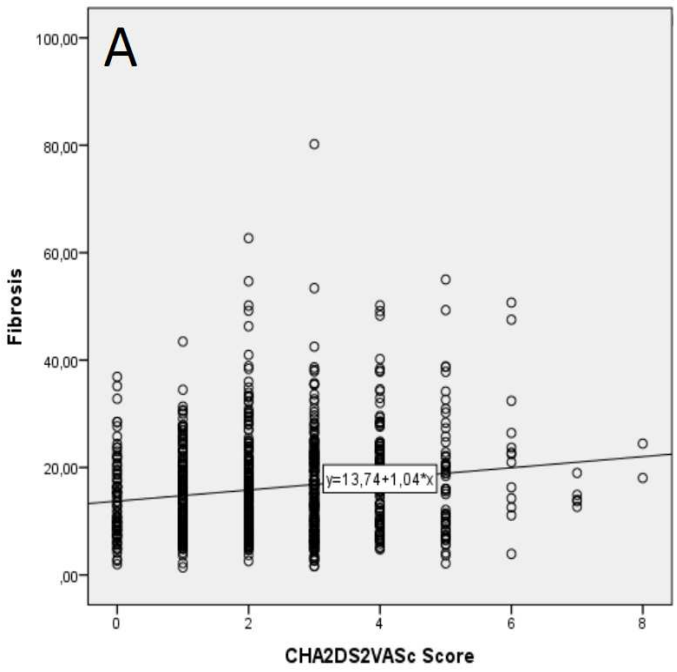


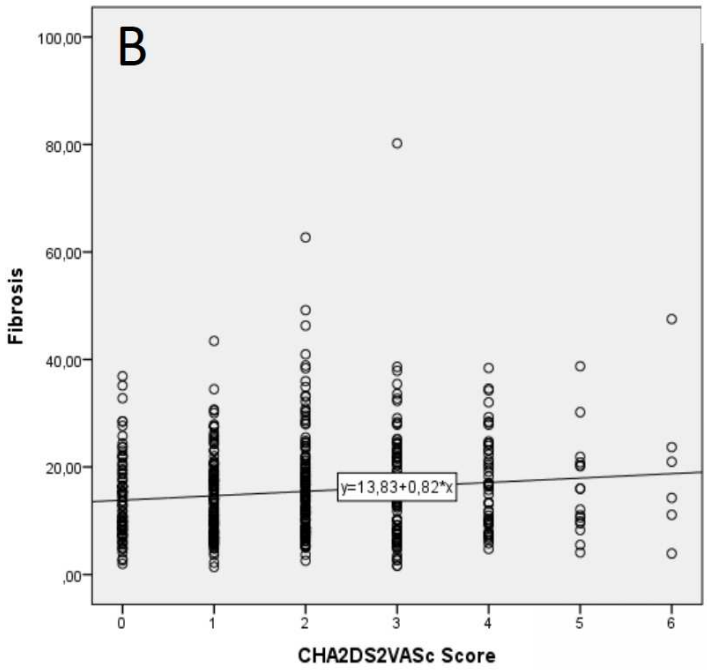
Figure 7. Left atrial fibrosis correlated with the CHA2DS2-VASc score.

2.2.7. The linear relationship between CHA2DS2-VASc and left atrial fibrosis

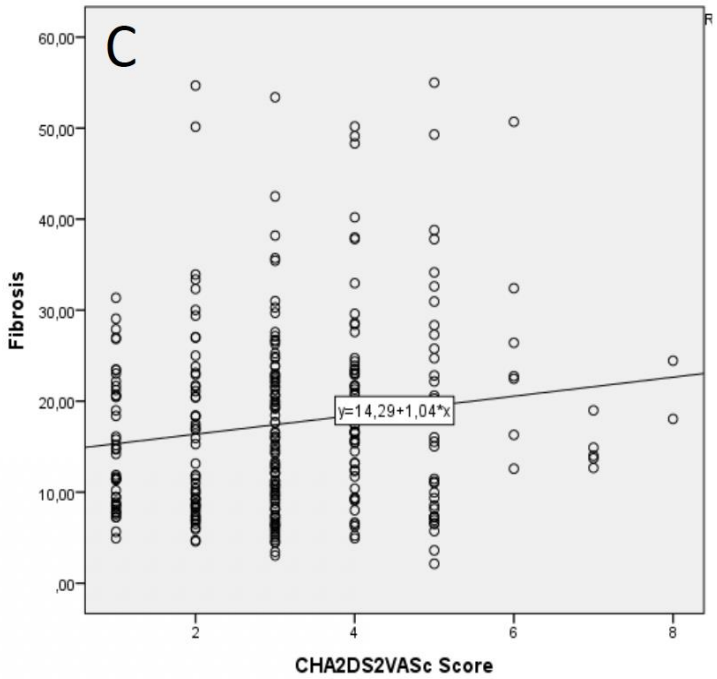
Regression analysis of fibrosis vs. CHA2DS2-VASc score shows a significant statistical association with fibrosis R= 0.025 x CHA2DS2-VASc + 1.94, P<0.0001; however, the R-squared value is 0.0268 indicating a poor correlation.



R^2 linear = 0.027



R^2 Linear = 0.015



R^2 Linear = 0.022

Figure 8. Linear relationship between CHA2DS2-VASc score and the left atrial fibrosis, A: the whole cohort (N= 836, 95 %CI 12.55%-14.92%, P= 0.0001), B: Male (N= 592, 95 %CI2.5%-15.15%, P= 0.0001), C: Female (N=316, 95 %CI1.5%-17.06%, P= 0.0006).

The CHA2DSVASc score and atrial fibrosis relationship was examined using a linear regression. This showed a statistically significant relationship. However, the correlation coefficient was low indicating that the predictive ability of the CHA2DS2VASc in assessment of atrial fibrosis is poor.

2.2.8. Univariate and multivariate associations of atrial fibrosis

The association of age, sex, and fibrosis were examined in a multi-variant linear regression model to determine whether the observed differences would remain significant. Female sex, persistent AF, time from AF diagnosis, and higher LA volume index were independently associated with higher fibrosis. The univariate and multivariate associations of fibrosis with other variables are detailed in Table 2.

Table 2 Univariate and multivariate correlations of atrial fibrosis

Variable	**Univariate B coefficient**	**P value**	**Multivariate B coefficient**	**P-value**
Age	0.11	<0.001	0,027	0.414
Female gender	2.25	0.001	2.48	0.002
Diabetes	1.82	0.038	0.281	0.773
Hypertension	1.06	0.123	-0.383	0.627
Coronary artery disease	1.91	0.018	1.44	0.120
Congestive heart failure	1.23	0.216	0.003	0.998
>1+ Mitral regurgitation (%)	1.93	0.134	0.467	0.733
Prior stroke (%)	2.45	0.020	1.5	0.183
Smoking history (%)	0.831	0.273	0.706	0.378
Obstructive sleep apnea	-0.227	0.775	-0.437	0.619
Body mass index (kg/m^2)	0.025	0.608	0.041	0.482
Persistent AF	3.11	<0.001	1.83	0.017
Median time from AF diagnosis	0.018	<0.001	0.016	<0.001
Prior anti-arrhythmic drug	0.451	0.348	0.321	0.459
LV ejection fraction (%)	-0.014	0.714	0.001	0.972
LA volume index (ml/m^2)	0.083	<0.001	0.s056	0.002

3.1. Discussion

The purpose of this study was to examine factors influencing the structural remodeling of the left atrium, with a particular focus on gender-specific differences, using a novel LGE-MRI approach for evaluating the atrial fibrotic substrate. With advancing age, we find higher amounts of fibrosis in the left atrium. We also found women to have a higher atrial fibrosis burden than men, particularly among those who had an ischemic stroke.

The population investigated in our present study shows similar patient characteristics compared with earlier trials. Men were also found to have a higher prevalence of OSA compared to women (54).

3.1.1. Left atrial changes in patients with atrial fibrillation

Relatively early animal experiments have shown that AF contributes to the left atrium's most severe electrical, functional, and structural changes (54). Research is currently focused on understanding the origins and evolution of such systemic changes. We note that AF itself induces atrial remodeling leading to AF's preservation, progression, and sustainability (56,57,58). The individual processes here are very complex, affecting primarily the ion channels and are not completely understood. Changes in the ion-channel are likely to lead to AF stabilization and early recurrence following cardioversion. Atrial ectopy includes Ca^{++}-handling defects, and atrial fibrosis is critical for the progression of long-term, persistent AF to permanent, resistant forms (59). It is also well known that atrial myopathy caused by AF has changes that depend on the duration of AF. (56)

Besides AF, disorders (such as hypertension, heart failure, diabetes, and myocarditis) or other factors (such as aging and endocrine abnormalities) are known to cause or lead to cardiomyopathy in the atria. However, the changes caused are not inherently disease-specific and instead share several similarities (59,60). The degree of pathological changes can vary over time and position within the atrium, resulting in substantial differences, both intraindividual and interindividual (53).

3.1.2. Imaging techniques to assess left atrial structural changes

In modern cardiology, different imaging methods are used to visualize the LA and diagnose potential cardiomyopathy in patients with AF. A consensus study on multimodality imaging for AF patients recently discusses in more detail the current state of atrial imaging (60). The following LA imaging methods are currently available and established: echocardiography, doppler echocardiography, strain imaging, cardiac computed tomography, and magnetic resonance imaging of the LA.

For the atrial size assessment, the most widely reported method is the linear dimension in the parasternal long-axis view using M-mode or two-dimensional echocardiography. However, due to the complex 3D nature of the atrium and the non-uniform nature of atrial remodeling, this measurement frequently does not provide an accurate picture of LA size (64). LA function can be assessed by pulsed-wave Doppler measurements of late diastolic filling. Multiple studies have used this parameter as an index of LA function assessment, but it is affected by age and loading conditions (65). Two-dimensional speckle-tracking echo has been used as a more sensitive marker to detect early functional remodeling before anatomical alterations occur (66,67).

Strain and strain rate imaging provides data on myocardial deformation by estimating spatial gradients at myocardial velocity (68,69). This approach was used as a surrogate for LA structural remodeling and fibrosis. Cardiac computed tomography (CCT) may be used for the precise measurement of atrial volumes. Volumetric data from CCTis comparable to data provided by CMR and 3D echocardiographic imaging and is superior to 2D echocardiography.

For the current research, we have used cardiac MRI for direct visualization of LA cardiomyopathy. The limited supply of MRI and high costs are still a barrier for use in clinical practice in many countries. However, the evidence for this imaging technique for evaluating LA structural changes tends to be superior to the approaches mentioned above.

3.1.3. The role of cardiac MRI for assessment of LA structural remodeling

CMR was used in clinical and research settings to provide gold standard volumetric chamber structure and function measurements. Contrast-enhanced CMR with gadolinium has recently been used as a tool for detecting atrial fibrosis (70). Even if these approaches are still in

relatively early stages and have not been widely established, the ability to recognize early stages of atrial structural change will undoubtedly improve our ability to detect varying degrees of remodeling that may not be as evident from the volumetric or functional assessment. In addition to LGE-MRI to identify replacement fibrosis, post-contrast T1 mapping (71,72) was used to measure diffuse interstitial fibrosis. Both techniques were associated with bipolar voltage calculated during invasive mapping (70).

Using a systematic evaluation system for the degree of delayed progress, a recently published multicenter study linked the degree of fibrosis observed by LGE CMR to the outcome of AF ablation (73). The risk of recurrent AF increased from 15% for Utah I (according to the Utah classification of atrial fibrosis (10 percent of the atrial wall) to 69% for Utah IV fibrosis (≥30 percent of the atrial wall). The authors proposed that CMR fibrosis quantification can play a role in the correct selection of patients most likely to benefit from AF ablation. Late-gadolinium-enhanced CMR has also been used to predict the incidence of sinus node dysfunction (74), stroke risk (75), and AF progression from paroxysmal to persistent (53).

It should be noted that these techniques need specialized software solutions for post-image processing. The MRI and post-image processing methods used in this study were the same as those used in the multicenter DECAAF trial (73). The MRI techniques used by various clinical centers to evaluate LA fibrosis are similar to those used in this study.

In addition to Corview for post-processing, two more specialized software packages are used to test atrial fibrosis, Itk-SNAP Version 2.2.0 (76) and QMass MR Software Version 7.2 (Medis Medical Imaging Systems, Leiden, Netherlands) (76). The most significant difference between LA fibrosis evaluation centers is how the LGE images are processed to measure LA fibrosis. Most of these centers use manual or semi-manual approaches to the LA wall segmentation of LGE images. LGE-MRI obtained at the same cardiac, and respiratory phases as 3D LGE-MRI can simplify the segmentation of the endocardial surface of LA. Some groups' evaluation of LA fibrosis, which analyzes the signal strength distribution of the segmented LA walls, is reliant on an expert decision to choose detection thresholds, which usually range from 2 to 4 SDs above normal myocardium (78).

Due to this visualization technique, by way of the most critical quantification of LA fibrosis only being used in a few centers of regular clinical practice together with only a few post-processing software solutions available, the data reproducibility is often criticized. A few groups have described inter-observer heterogeneity of the LA fibrosis evaluation. The

Comprehensive Arrhythmia Research and Management (CARMA) Center reported inter-observer correlation coefficients in the range of 0.79 to 0.97, demonstrating high reproducibility concerning LA wall segmentation and fibrosis quantification (79, 81). Many experienced groups reported a correlation coefficient of 0.93 for LGE quantification, with a written inter-observer agreement of 0.96 (81). Such high correlation coefficients for observation variability indicate experience in acquiring good quality LGE-MRI data, reliable LA wall segmentation, and reproducible fibrosis quantification in high-volume centers. In summary, MRI has a high potential as a non-invasive diagnostic method for detecting LA structural changes without radiation exposure or risk of invasive treatment. However, it is essential to note that both LGE-MRI techniques and the post-processing evaluation of LA fibrosis require considerable expertise; thus, more technological advances and more comprehensive imaging methods need to be developed worldwide.

3.1.4. Gender-specific differences in cardiovascular diseases

Epidemiological and retrospective research of patients with AF revealed substantial differences between men and women. The lifetime risk of developing AF has been reported to be almost the same between men and women. However, after 75 years of age, about 60 percent of people with AF are female (82). In the AF Follow-up Rhythm Control Research (AFFIRM) study, women with AF were substantially older than men (83). In the Canadian Registry of AF, women were, on average, 5 years older than men at the time of the first ECG-confirmed AF diagnosis (84). Our study was comparable in baseline characteristics and comorbidities to major AF cohort studies. Our findings are consistent with the papers showing that female AF patients are substantially older than males (21,22,23). Men with AF have also been reported to have a higher burden of ischemic heart disease, whereas women have a higher burden of valvular heart disease (85). The population surveyed in our present research has been observed over eight years and has similar patient characteristics compared to previous studies. Men have also been shown to have a higher incidence of OSA and a significantly higher BMI than women.

The precise mechanism of origin and development of LA fibrosis in human AF is not understood. Animal studies have shown that persistent AF is associated with adverse atrial structure and function remodeling (86). In humans, the presence of AF is associated with higher rates of tissue fibrosis on microscopic examination (87) as well as with the LGE-MRI assessment (88). The relationship of fibrosis with age shows a positive correlation, suggesting

that age-related degeneration plays a role in the AF substrate progression. It is also reported that women typically experience longer and more symptomatic AF episodes, possibly induced by fibrosis and impairment of the AF substrate (89,90). Information on AF episodes has not been reported in our study. Potential contributing factors to AF include genetic and gender-related variations in protein expression between the two sexes. Men are known to have a higher expression of repolarizing ion-channel subunits that can contribute to shorter refractoriness and promote re-entry (55). The LA volume, indexed to body size, did not vary substantially between the sexes. In the total US population, the prevalence of hypertension among men is higher than among women. That association is retained below the age of 65; however, the prevalence of hypertension is higher in women after 65(51). This is believed to be due to a change in the hormonal balance after menopause. In our study, the history of hypertension (described as systolic blood pressure >140 or diastolic blood pressure >90mm Hg or 'yes' to anti-hypertensive medication) was equally prevalent among men and women. It is possible that this could have played a role in the disparities in fibrosis between the sexes in our cohort. The subgroup of patients over 80 years of age showed an insignificant, but interesting, reversal of the fibrosis and sex relationship. Men in this subgroup have had higher incidence of fibrosis than women.

3.1.5. Risk of stroke in women with atrial fibrillation

It has repeatedly been shown that the risk of AF-related stroke is increased in women and at an advanced age (81). Such parameters are taken into account in the CHA2DS2-VASc score. The mechanism of stroke in AF is still poorly understood. It is assumed that AF is associated with the Virchow triad of stasis, hypercoagulability, and tissue damage leading to thrombus formation. Finding higher atrial fibrosis in women, especially those with a history of ischemic stroke, may bring some important mechanistic insight into our understanding of the higher risk of thromboembolic stroke in women. Higher atrial fibrosis can contribute to thrombus formation by decreasing atrial contractile function. Likewise, higher atrial fibrosis was associated with decreased atrial mechanical function assessed echocardiographically by speckle tracking and assessment of atrial lateral wall strain and strain rate (91). Higher fibrosis can also elevate the risk of stroke by altering the atrial hemostatic environment, promoting thrombus formation. More recent research exploring the relationship between atrial arrhythmia episodes, like AF, detected by cardiac-embedded electronic devices have shown that device-detected episode timing does not always precede thromboembolic events (92). It is possible that fibrotic atrial disease, which causes atrial contractile dysfunction and hemostatic

alterations, can contribute to atrial thrombus formation and eventual embolization without necessarily manifesting clinical arrhythmia. Recent in vitro studies have also indicated that thrombin is associated with an inflammatory, pro-fibrotic state that contributes to the formation and enhancement of the atrial substrate (92). This demonstrates that atrial fibrosis and thrombus formation may be a two-way process.

In our study, patients with a previous stroke, particularly women, have higher fibrosis compared to other AF patients without a history of stroke (55). This suggests that sex may play a role in the fibrotic remodeling of the LA and subsequent stroke.

3.1.6. Study limitations

Our cohort was predominantly made up of white, non-Hispanic ethnicity. Atrial fibrosis evaluation has not been performed before on such a large scale. LGE-MRI, however, was not performed at the time of stroke and the average time from stroke to atrial fibrosis evaluation was almost 2 years. Ascertainment of whether these strokes were embolic or thrombotic in nature was also limited. Moreover, some AF patients who may have died, or suffered severe disability due to stroke, may not have presented for evaluation and therefore were not included in this study. The impact of other relevant factors like alcohol consumption, atherosclerosis, and hyperthyroidism on atrial fibrosis wasn't also accessed in this work. We consider this a limitation because of the reported role of those factors in the left atrial remodeling (5).

3.1.7. Scientific achievement

Modern imaging methods like LGE-MRI help to determine early LA remodeling and the level of LA fibrosis. As shown in this investigation, the CHA2DS2-VASc Score correlates poorly with LA fibrosis while LGE-MRI effectively unveils not only LA fibrosis, but also the risk of AF and stroke, encouraging changes in the actual guidelines (suggesting CHA2DS2-VASc Score as the only indicator of stroke risk); LGE-MRI-detected LA fibrosis should be accepted as a strong predictor of AF and stroke.

More advanced fibrosis detected in women suggests that sex may play a role in fibrotic remodeling of the LA and subsequent stroke. Since our results have shown more LA fibrosis

in women compared to men, the risk of stroke in female patients may be underrated in actual guidelines.

Affordability and cost may limit the integration of this method into the daily routine of risk assessment. Nevertheless, if our results are confirmed by larger randomized trials and included in practice guidelines, earlier detection of patients at elevated AF risk and better stroke prevention might be enabled.

Furthermore, the submitted data may become another step towards personalized medicine in modern cardiology.

3.2. Conclusion

Atrial fibrosis quantification using LGE-MRI confirms that aging female patients with atrial fibrillation have more advanced fibrosis than their male counterparts. These sex differences are more pronounced with a stroke history, suggesting that sex may play a role in the fibrotic remodeling of the LA and subsequent stroke. Women with a prior history of stroke also have higher fibrosis compared with both women and men without a history of stroke. Advanced fibrosis may explain the female and age association with stroke in AF. As no correlation between the LA fibrosis and CHA2DS2-VASc Score was detected in this work, we suppose that LGE-MRI should always be used in the assessment of atrial remodeling.

Abstract in Croatian language

Razlike u fibrozi atrija po dobi i spolu među pacijentima s atrijskom fibrilacijom

Cilj: Dob i ženski spol povezani su s većim rizikom za moždani udar u osoba s atrijskom fibrilacijom (AF). Željeli smo utvrditi jesu li starija životna dob i ženski spol povezani s višom razinom fibroze atrija.

Metode i rezultati: Proveli smo kohortnu studiju u koju smo uključili pacijente s AF koji su bili upisani u bazu podataka na Sveučilištu Utah i kontrolnu skupinu bez AF, koja je podvrgnuta magnetskoj rezonanciji s kasnim gadolinijskim kontrastnim pojačanjem prikaza (engl. late-gadolinium enhancement magnetic resonance imaging, LGE-MRI) radi određivanja atrijske fibroze. Osobe s kontraindikacijama za LGE-MRI pretragu su bile isključene. Devet stotina i osam uzastopnih ispitanika muškog i ženskog spola s AF i 15 kontrola bez AF-a bilo je uključeno u ovo istraživanje. Fibroza lijevog atrija se povećavala s dobi i kod muškaraca i kod žena s AF. Žene s AF (n=316) bile su starije od muškaraca (n=592), s prosječnom dobi od 68,7 godina ± 11,6 u odnosu na 64,9 ± 11,7 godina u muškaraca (P<0,001) te su imale višu razinu fibroze lijevog atrija u usporedbi s muškarcima (17,5 ± 10,1% nasuprot 15,3 ± 8,9%; P<0,001). Žene su također imale veću prevalenciju prethodnog moždanog udara u usporedbi s muškarcima (15,8% nasuprot 6,5%; P<0,001). Dob i spol bili su prediktori atrijske fibroze u multivarijatnoj analizi. U usporedbi s kontrolnom skupinom koja nema AF, pacijenti s AF imali su značajno višu razinu atrijske fibroze (16,0 ± 9,4 naspram 5,5 ± 5,8%; P<0,001).

Zaključci: Starija životna dob i ženski spol povezani su s većim teretom atrijske fibroze kod pacijenata s AF. Žene koje imaju prethodni moždani udar također imaju i veću razinu atrijske fibroze u usporedbi sa ženama i muškarcima koji nisu imali moždani udar. Uznapredovala fibroza može objasniti povezanost između ženskog spola i starije životne dobi s moždanim udarom kod AF.

Abstract and title in English language

Age and sex differences in atrial fibrosis among patients with atrial fibrillation

Aim Age and female sex are associated with a higher risk of stroke in atrial fibrillation (AF). We sought to determine whether advancing age and female sex are associated with higher atrial fibrosis.

Methods and results We conducted an observational cohort study of patients with AF enrolled in the University of Utah AF Database and a non-AF control group who underwent late-gadolinium enhancement magnetic resonance imaging (LGE-MRI) for atrial fibrosis quantification. Participants with contraindications for contrast MRI scanning were excluded. Nine hundred and eight consecutive men and women with AF and 15 non-AF controls were included in this study. Left atrial fibrosis increased with age in both men and women with AF. Women with AF (n = 316) were older than men (n = 592): mean age 68.7±11.6 vs. 64.9±11.7 years; $P < 0.01$, and had higher left atrial fibrosis compared with men 17.5 ± 10.1% vs. 15.3 ± 8.9%; $P < 0.001$. Women also had a higher prevalence of prior stroke than men (15.8% vs. 6.5%; $P < 0.001$). Age and sex relationships with atrial fibrosis remained significant in multivariate analysis. Compared with the non-AF control group, patients with AF they had significantly higher atrial fibrosis: 16.0 ± 9.4 vs. 5.5 ± 5.8%; $P < 0.001$.

Conclusions Advancing age and female sex are associated with a higher burden of atrial fibrosis in patients with AF. Women with a prior history of stroke also have higher fibrosis than women and men without a history of stroke. Advanced fibrosis may explain the female and age association with stroke in AF.

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Doctoral thesis

University of Kiel, Medical School – Department of Physiology

•Brain activity during simple and complex finger movements – a fMRI study,

(Magna cum laude)

Mentor: Prof. Dr. med. Johann Kuhtz-Buschbeck

Publications

First- and Senior authorship

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Co-Authorship

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