



Gender-differences in prevalence and outcome of ischemic stroke and promoting factors of atrial thrombi

Karsten Keller^{a,b,*}, Martin Geyer^{b,d}, Thomas Münzel^{b,a,c},
Mir Abolfazl Ostad^b

^a Center for Thrombosis and Hemostasis (CTH), University Medical Center Mainz (Johannes Gutenberg-University Mainz), Mainz, Germany

^b Center for Cardiology, Cardiology I, University Medical Center Mainz (Johannes Gutenberg-University Mainz), Mainz, Germany

^c German Center for Cardiovascular Research, Partner site Rhein-Main, Mainz, Germany

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Abstract *Background:* Ischemic stroke is an important cause of death and disability. However, data about gender-differences in stroke are controversial.

Methods: In the nationwide sample, male and female inpatients were selected by screening for ischemic stroke by ICD-Code(I63) and compared. In a second study, we performed a retrospective analysis of patients who underwent transesophageal echocardiography (TEE) and screened for gender specific associations between clinical and echocardiographic parameters and atrial thrombi formation.

Results: Males had a higher incidence of ischemic stroke than females (372 vs. 340 per 100,000 citizens) with a substantial age-depending increase. Percentage of stroke patients with atrial fibrillation/flutter (AF, 34.2% vs. 26.5%) and the case-fatality rate (9.4% vs. 7.1%) were higher in females. AF seems to aggravate stroke events. In the retrospective study, 227 patients were enrolled (87 females (38.3%)). Females were older (IQR 72.0 (72.0–79.0) vs. 66.5 (57.3–76.8) years, $P = 0.013$), showed smaller right atrial (RA) area and slower blood flow velocity in left atrial appendage (LAA) (41.2 (29.2–58.5) vs. 50.0 (34.3–67.1) $\text{cm}^3\text{sec}^{-1}$, $P = 0.038$). Promoting factors of atrial thrombi in both genders were lower blood-flow velocity in LAA, larger LAA diameters, higher $\text{CHA}_2\text{DS}_2\text{VASc}$ -score and heart failure. AF, larger atrial septal-lateral diameters and areas were associated with atrial thrombi especially in males.

Conclusions: Our study demonstrated gender-specific differences in ischemic stroke. Incidence of ischemic stroke was higher in males than in females increasing exponentially with growing

* Corresponding author. Center for Thrombosis and Hemostasis (CTH), University Medical Center Mainz Johannes Gutenberg-University Mainz, Langenbeckstrasse 1, 55131, Mainz, Germany. Fax: +0049 6131 17 8461.

E-mail address: Karsten.Keller@unimedizin-mainz.de (K. Keller).

^d K.K. and M.G. contributed equally and should both be considered as first authors.

age in both genders. Females had a higher case-fatality rate presumably due to higher rate of AF. Promoting factors of atrial thrombi differ especially regarding atrial volumes and blood flow velocity in the LAA.

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Introduction

Ischemic stroke is an important cause of death and disability worldwide in men and women.^{1–8} While its incidence in low- and middle-income countries has doubled during the last 40 years, it declined in the high-income countries by approximately one third.^{2,9} Overall, the incidence of stroke rises exponentially with increasing age.^{1,7,10–13} However, data about gender-differences in stroke and its outcomes are conflicting.⁸

Sex-specific differences in cardiovascular diseases (CVD) are well recognized.^{14–19} In general, male sex is connected with both an increased risk of both developing CVD as well as fatal outcome.²⁰ While some studies reported a higher proportion of female stroke patients,²¹ other studies showed a higher incidence of ischemic stroke in males.^{1,16} Although women and men share most of the cardiovascular risk factors and comorbidities, the importance of these factors and comorbidities in stroke patients of both sexes are different.^{8,22} In accordance with other manifestations of cardiovascular disease, women are older at the ischemic stroke event^{23,24} and female and male stroke patients differ significantly in presentation of symptoms and outcomes.^{8,22} In females, imaging diagnostic procedures and carotid surgery are less frequent and some studies additionally report on a more restricted use of thrombolytic treatment as well as a less favourable outcome.^{22,25–28} The mortality risk increases significantly with growing age.²⁷

Cardio-embolic stroke events account for about one fifth of ischemic strokes²⁹ and patients with atrial fibrillation have a 3- to 5-fold elevated relative risk for occurrence of stroke in comparison to individuals without.^{3,30} Thromboembolic strokes due to atrial fibrillation are frequently devastating, leading to severe impairment or death in the majority of patients.^{29,31,32} The left atrial appendage (LAA) harbors approximately 90% of intra-cardiac thrombi in atrial fibrillation.¹³

Thus, the objectives of this study were to elucidate gender-specific differences in ischemic stroke in the nationwide sample and to identify gender-differences in atrial thrombi development.

Methods and patients

Two separate patient cohorts were analyzed

1. German nationwide cohort with analysis for predictors of death in ischemic stroke patients

The German nationwide in-patient statistics (Diagnosis related groups (DRG statistics)) of the year 2015 was used

for this first analysis. The information includes treatment data from all inpatients processed according to the DRG system. In Germany, diagnoses of inpatients are coded according to ICD-10-GM (International Classification of Diseases, 10th Revision with German Modification). DRG-coded diagnoses data are gathered at the Federal Statistical Office in Germany (Statistisches Bundesamt, DEStatis). In the year 2015, overall 19.2 million in-patient files from 1956 hospitals were registered. For this analysis, mortality data of in-patients diagnosed for ischemic stroke (ICD code I63) with and without additionally coded atrial fibrillation/flutter (AF) (ICD code I48) stratified for gender were obtained from the Federal Statistical Office of Germany (Statistisches Bundesamt, DEStatis, source: DRG-Statistik, Sonderauswertung des Statistischen Bundesamtes). Since this study part did not involve direct access by the investigators to data on individual patients but only to summary results provided by the Research Data Center, approval by an ethics committee and informed patient consent were not required according to German law.

2. Single center cohort at the University Medical Center Mainz for the analysis regarding the correlation between echocardiographic parameters and clinical features on the one hand and atrial thrombi as the source of cardioembolic stroke on the other hand

Patients who underwent a transthoracic echocardiography (TEE) at the Center of Cardiology of the University Medical Center Mainz (Mainz, Germany) were included in this retrospective analysis. This cohort included consecutive patients, aged ≥ 18 years, who were examined in the echocardiography department of the Center of Cardiology (accredited echocardiography institution by the European Society of Cardiology) by TEE between January and March 2013. Patients were stratified by gender in the two subgroups of female and male patients.

We assessed patients' anthropometric and clinical characteristics, comorbidities and echocardiographic parameters. The CHA₂DS₂-VASc-score (Congestive heart failure, Arterial Hypertension, Age ≥ 75 years, Diabetes mellitus, prior ischemic Stroke, TIA or thromboembolism, Vascular disease, Age 65–74 years, female sex (but female sex is only a risk factor if other risk factors are also present))³³ was calculated for all patients. Echocardiographic measurements were obtained by evaluation of two- and three-dimensional TTE and TEE loops stored on the clinic's server in DICOM-standard and assessment via Philips Xcelera[®] and Qlab[®] software (trademark by Philips[®] healthcare). All echocardiographic analyses were performed and confirmed by at least two experienced echocardiographers. The echocardiographic measurements

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