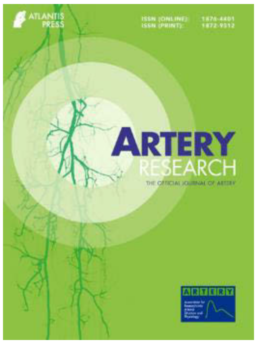

Artery Research

ISSN (Online): 1876-4401 ISSN (Print): 1872-9312
Journal Home Page: https://www.atlantis-press.com/journals/artres

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

Karsten Keller, Martin Geyer, Thomas Münzel, Mir Abolfazl Ostad

To cite this article: Karsten Keller, Martin Geyer, Thomas Münzel, Mir Abolfazl Ostad (2018) Gender-differences in prevalence and outcome of ischemic stroke and promoting factors of atrial thrombi, Artery Research 22:C, 68–78, DOI: https://doi.org/10.1016/j.artres.2018.05.004

To link to this article: https://doi.org/10.1016/j.artres.2018.05.004

Published online: 3 December 2019

Artery Research (2018) 22, 68–78

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/artres

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

Karsten Keller [a,b,*,d], **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*

Received 23 March 2018; received in revised form 2 May 2018; accepted 7 May 2018
Available online 26 May 2018

KEYWORDS
Ischemic stroke;
Sex;
LAA;
Left atrial appendix;
Gender;
Atrial fibrillation;
Mortality;
Stroke

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) cm*sec^{-1}, $P = 0.038$). Promoting factors of atrial thrombi in both genders were lower blood-flow velocity in LAA, larger LAA diameters, higher CHA_2DS_2-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.

https://doi.org/10.1016/j.artres.2018.05.004

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.

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 strokes[29] 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] Thrombo-embolic 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 cardio-embolic 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 CHA_2DS_2-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 comprised evaluation of thrombogenic material, which was defined as the presence of solid thrombi or relevant spontaneous echo contrast (SEC) in the LAA, blood flow velocity in LAA detected by Pulsed-waved (PW—)Doppler as well as the spatial dimensions of the LAA in kind of width (septal-lateral diameter obtained in short axis view/45° angulation) and length (aperture-apex) of the LAA in TEE (Fig. 1). Confirmation or exclusion of atrial thrombi or SEC was performed in all recorded angulations and three-dimensional reconstructions, if available.

Left ventricle ejection fraction (LVEF), left and right septal-lateral and longitudinal diameters as well as atrial areas and systolic pulmonary artery pressure were measured, if a TTE was available (from the same hospital visit). Ventricular dimensions, LVEF and atrial areas were determined in apical 4 chamber view using Simpson's method according to the EACVI- and ASE-recommendations on cardiac chamber quantification.[34] Proposed systolic artery pressure (sPAP) was estimated from Doppler regurgitation velocity on tricuspid regurgitation (Fig. 1).

Since the study involved only an anonymous, retrospective analysis of diagnostic standard data, ethics approval was not required according to German laws.

Statistics

First, we calculated the incidence of ischemic stroke for the German male and female citizens overall and stratified by age-groups in the year 2015. The proportion of ischemic stroke patients with additionally diagnosed AF and the relative mortality rate in female and male ischemic stroke patients was computerized stratified by age groups. Moreover, we calculated the mortality rate in all ischemic stroke patients, patients with and without additional AF in females relative to males 2015 in Germany stratified by age groups. The mortality rate of the males was taken as reference group and equal mortality rate in both genders was equated with 1.

In the second mono-centric retrospective study cohort, we compared male and female patients who underwent a TEE due to different reasons.

Descriptive statistics for the relevant baseline comparison of both genders are provided with mean ± standard deviation, median and interquartile range (IQR), depending on Gaussian or skewed distribution, or absolute numbers and corresponding percentages. Continuous variables found not to follow a normal distribution, when tested with the modified Kolmogorov—Smirnov test (Lilliefors test), were compared using the Wilcoxon-Whitney U test. Normal distributed continuous variables were compared using the Students' T-Test and categorical variables with Fisher's exact or Chi^2 test, as appropriate.

We calculated univariate logistic regression models to examine the associations between thrombogenic material and parameters such as age, sex, body height, weight, body-mass-index, echocardiographic measurements and comorbidities (inclusively AF), respectively.

The parameters CHA$_2$DS$_2$Vasc-score, LAA longitudinal diameter, left and right atrial area, which were respectively associated with thrombogenic material, were entered in a receiver operating characteristics (ROC) analysis and a cut-off value for these parameters were calculated.

The software SPSS® (version 22.0; SPSS Inc., Chicago, Illinois) was used for the majority of computerised analysis. Only P values of <0.05 (two-sided) were considered to be statistically significant.

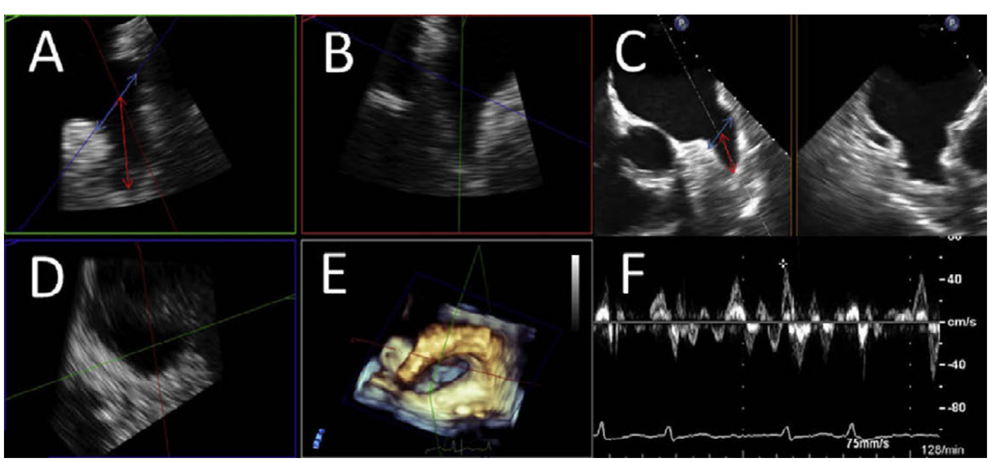

Figure 1 Assessment of LAA diameters and LAA velocity. LAA expansions were measured by determining orifice width and LAA depth. LAA orifice width (marked as red arrow) was estimated by measuring septo-lateral diameter in short axis view (SAX) as an approximated plane from the left coronary height (septal) to 1—2 cm below the highest point of the LUPV (left upper pulmonary vein)-limbus ("rim"/lateral); LAA depth (marked as blue arrow) was determined as distance from orifice plane to the deepest point of the LAA. If available, measurements were performed by multi-planar reconstruction of three-dimensional echo loops (Panels A, B, D: Panel A shows a reconstructed plane resembling SAX-view in left upper quadrant, Panel B another reconstructed longitudinal plane orthogonal on Panel A, Panel D the reconstructed "orifice" of the LAA). Panel C demonstrates measurements in "conventional" 2-dimensional TEE at about 45° resembling SAX-view. Panel E shows spatial relations in the LA in a three-dimensional overview in "non-surgical" orientation. Panel F shows the determination of blood velocity in the LAA via PW-doppler in a patient with present atrial fibrillation (obviously shown by PW-curve demonstrating rapid and irregular LAA contractions).

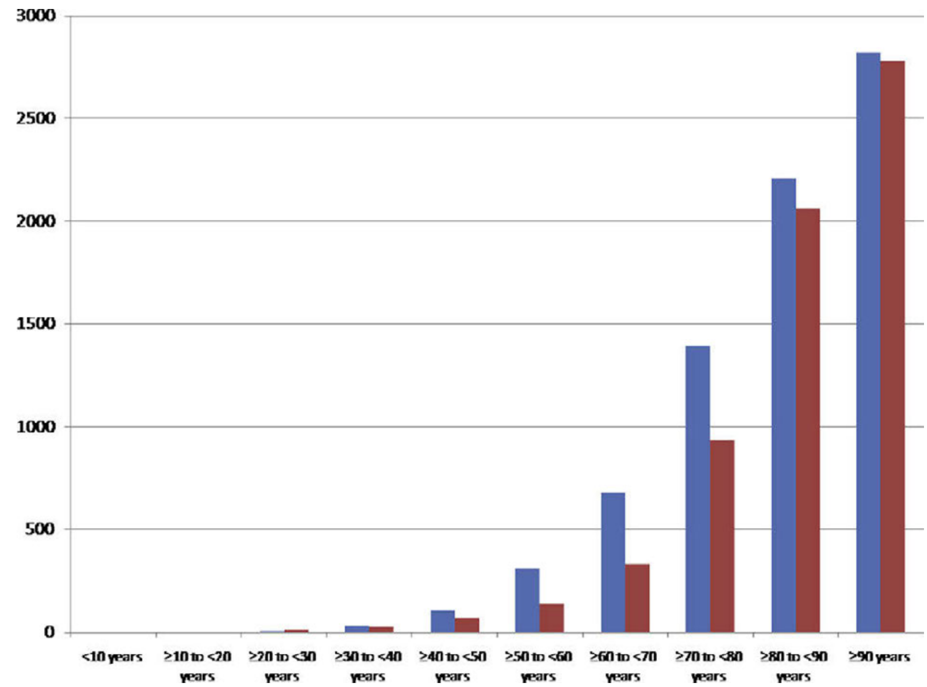

Figure 2 Incidence of ischemic strokes (ICD-code I63) in women (red bars) and men (blue bars) 2015 in Germany stratified by age groups. (For interpretation of the references to color/colour in this figure legend, the reader is referred to the Web version of this article.)

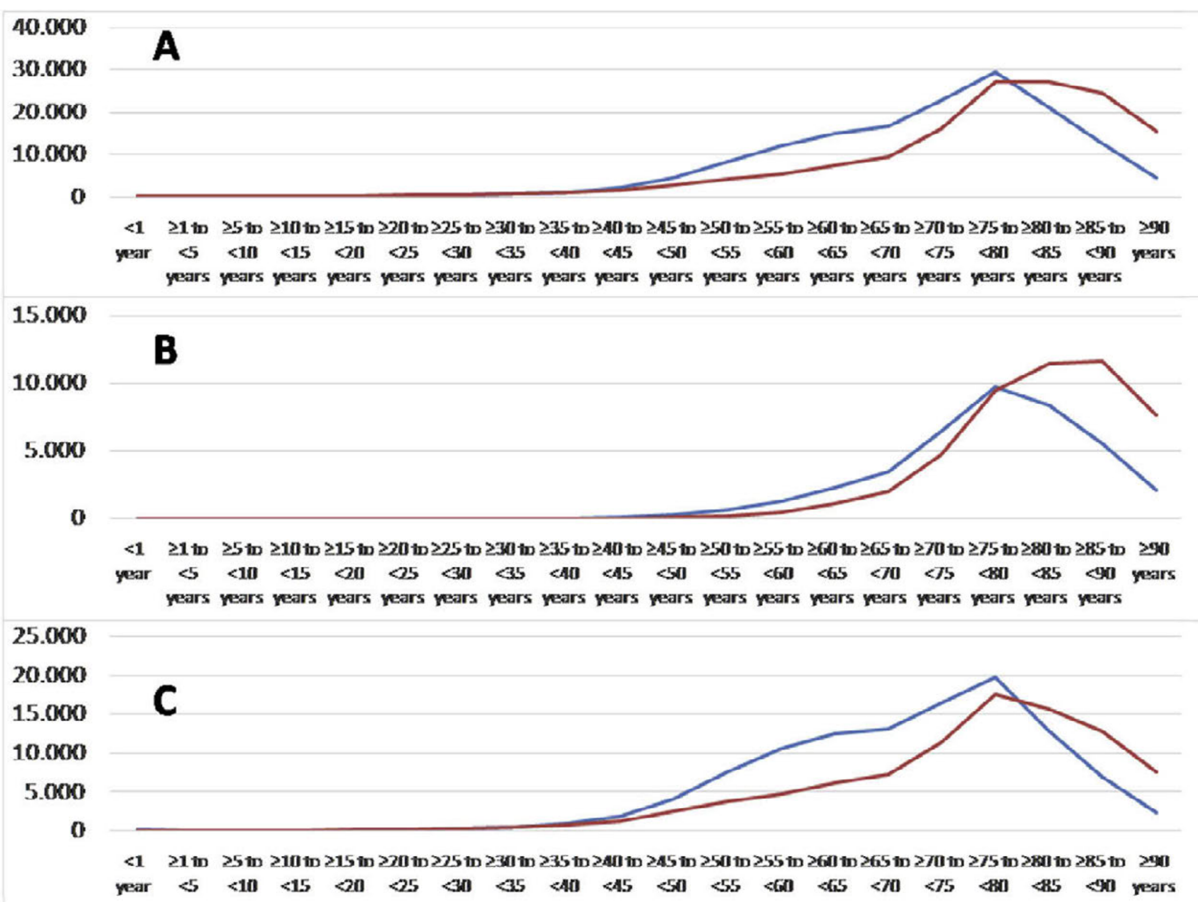

Figure 3 Total numbers of ischemic strokes (ICD-code I63) in women (red lines) and men (blue lines) 2015 in Germany stratified by age groups: overall (A), with (B) and without additional atrial fibrillation (C). (For interpretation of the references to color/colour in this figure legend, the reader is referred to the Web version of this article.)

Results

Analysis of age-dependence and the predictors of death in ischemic stroke patients

The nationwide sample comprised 150,595 male and 141,801 female inpatients with ischemic stroke in Germany 2015. The incidence of ischemic stroke was 372 per 100,000 individuals in males and 340 per 100,000 individuals in females. Total numbers as well as the incidences of ischemic stroke events increased with growing age in both genders (Figs. 2 and 3). Also the proportion of stroke patients with diagnosed AF inclined exponentially with growing age in males and females (Fig. 4A). Interestingly, the percentage of female stroke patients with diagnosed AF was distinctly higher than in male patients (34.2% vs. 26.5%).

In total, 10,715 male and 13,336 female patients with ischemic stroke died in-hospital. Therefore, the case-fatality rate was relevantly higher in females than in males (9.4% vs. 7.1%). The relative mortality rate increased in both genders with growing age (Fig. 4B).

AF seems to aggravate stroke events especially after the 75th life-year significantly (Fig. 5).

Correlation between echocardiographic parameters, clinical features and atrial thrombi potentially induce ischemic stroke

In total, 227 consecutive patients who underwent TEE for various reasons were enrolled for this analysis. Among these patients 140 were of male and 87 of female gender. The medical indications for TEE comprised i) evaluation regarding intra-cardiac thrombogenic material before planned cardioversion in 58.2% of the females and 65.2 of the males, ii) further evaluation of valve disorders (including suspected endocarditis) in 32.2% of the women and 32.9% of the men, as well as iii) other reasons in 9.6% of the female and 1.9% of the male patients.

The clinical characteristics and echocardiographic parameters of the patients stratified for gender were presented in Table 1. Briefly, females were older at the examination date (72.0 (IQR 72.0—79.0) vs. 66.5 (57.3—76.8) years, $P = 0.013$), and as expected, less tall (1.64 ± 0.08 vs. 1.77 ± 0.08 m, $P < 0.001$) and weight less (69.0 (62.0—80.0) vs. 84.0 (73.0—95.0) kg, $P < 0.001$) than their male counterparts, while the BMI was similar between both subgroups.

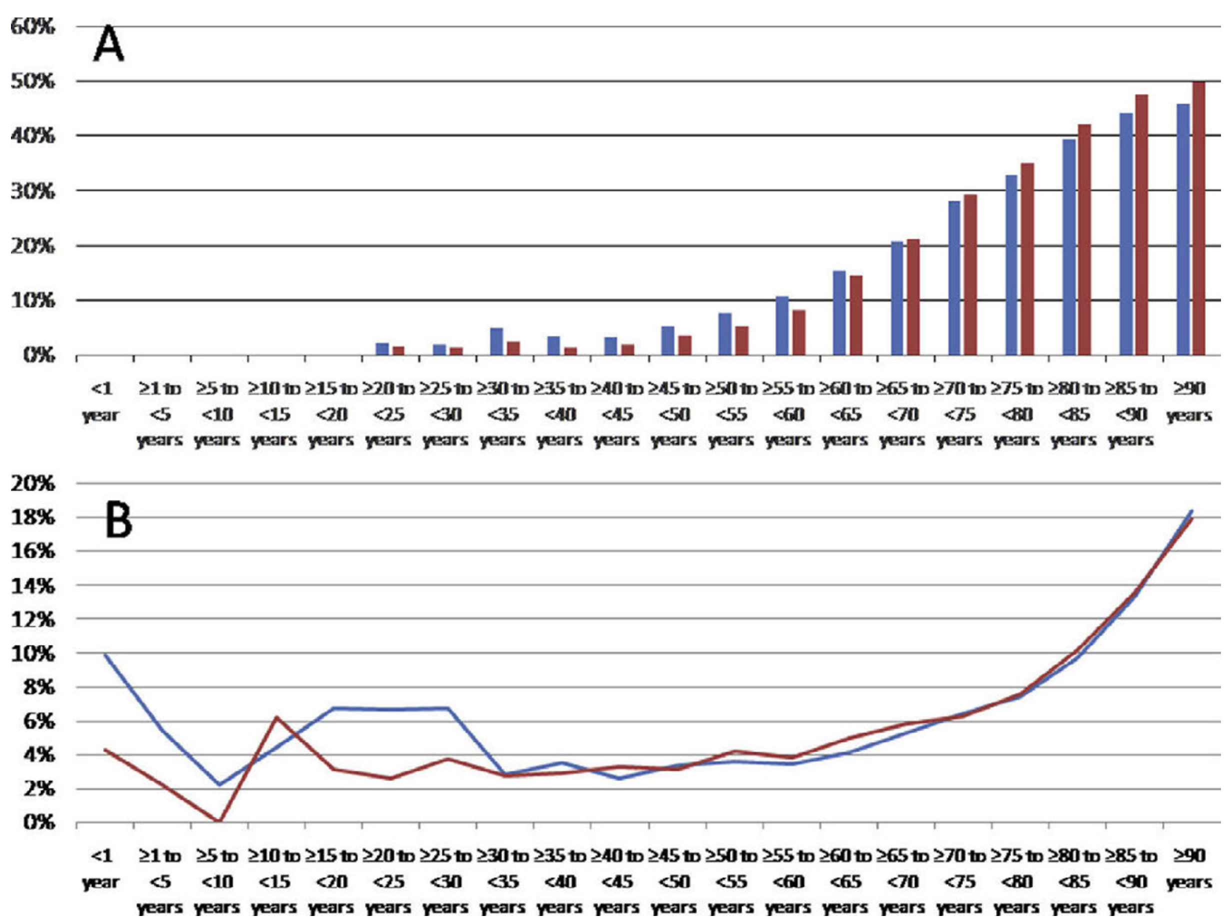

Figure 4 (A) Proportion of ischemic stroke patients diagnosed with atrial fibrillation in men (blue bars) and women (red bars) 2015 in Germany stratified by age groups. (B) Relative mortality rate in female (red line) and male (blue line) ischemic stroke patients 2015 in Germany (percentage of in-hospital mortality for the different age groups). (For interpretation of the references to color/colour in this figure legend, the reader is referred to the Web version of this article.)

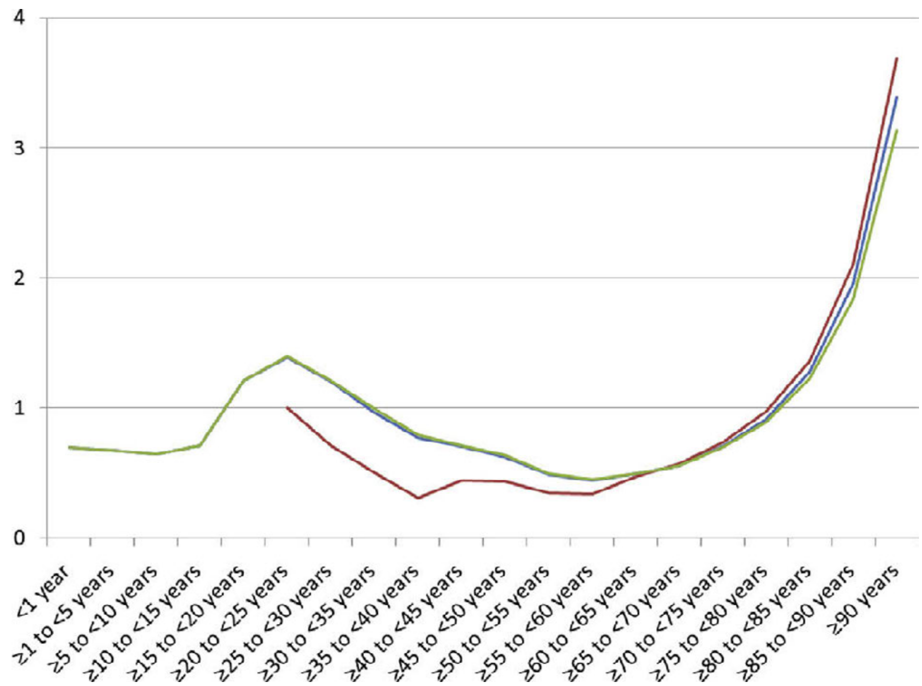

Figure 5 Mortality rate in all ischemic stroke patients (blue line), patients with additional atrial fibrillation (red line) and without additional atrial fibrillation (green line) in females relative to males 2015 in Germany stratified by age groups. Equal mortality rate in both genders is equated with 1. Values > 1 represent higher mortality rate in women. (For interpretation of the references to color/colour in this figure legend, the reader is referred to the Web version of this article.)

Regarding comorbidities, females showed higher frequency of prior deep venous thrombosis (DVT, 12 (13.8%) vs. 6 (4.3%), P = 0.020) in their medical history, but not pulmonary embolism (PE, P = 0.512). While thrombogenic material (solid thrombus material and spontaneous echo contrast) in the LAA was similar often identified in both genders (P = 0.197), solid thrombi were more often identified in females (5.2% vs. 0%, P = 0.026).

Echocardiographic measures revealed a larger right atrial (RA) area in males, whereas all LA parameters, inclusively the LAA measurements were not significantly larger in men compared to women. Interestingly, the blood flow velocity in the LAA detected by Pulsed-waved Doppler was higher in male than in female patients (50.0 (34.3–67.1) vs. 41.2 (29.2–58.5) $cm*sec^{-1}$, P = 0.038).

Promoting factors of atrial thrombi (solid thrombus or SEC) in both genders were a lower blood flow velocity in the LAA, a larger LAA diameter, a higher CHA_2DS_2-VASc-score and the comorbidity of heart failure (Table 2). Additionally, larger left and right atrial septal-lateral diameters and areas were also associated with atrial thrombogenic material in male patients, but not in females.

The ROC analyses confirmed the regression results. The best diagnostic performance of the parameters was observed for LA area in prediction of atrial thrombogenic material with an AUC of >0.8 in males and for LAA longitudinal diameter with an AUC of >0.7 in females (Table 3, Fig. 6), whereas the AUC values for the CHA_2DS_2-VASc-scores of women and men were similar.

Discussion

Ischemic stroke is a major cause of death and disability in both genders[1–8] and especially the subgroup of cardio-embolic strokes due to AF is often accompanied by a poor outcome with severe impairment or death.[29,31,32] Study results about gender-specific differences and aspects of ischemic stroke are inconsistent.[8,35] Thus, the objectives of this study were to elucidate gender-specific differences in ischemic stroke in the German nationwide sample and to identify gender-specific differences in atrial thrombi development.

The main findings of our study can be summarized as follows: I) the incidence of ischemic stroke was higher in male than in female citizens of Germany and II) it inclined dramatically with age in both genders. III) AF as additional diagnosis was more frequent in female stroke patients. IV) The case-fatality rate during in-hospital course was distinctly higher in females compared to males and V) the mortality rate increased in both genders with age. VI) Regarding cardio-embolic stroke, lower blood flow velocity in the LAA, larger LAA diameter, higher CHA_2DS_2-VASc-score and heart failure promoted atrial thrombi in both genders, while VII) AF, diabetes, larger left and right atrial septal-lateral diameters and areas were associated with atrial thrombogenic material especially in males.

Incidence of ischemic stroke

In accordance with the literature, the incidence of ischemic stroke was higher in male than in female citizens

Table 1 Clinical characteristics and echocardiographic parameters in female and male patients.

Variable	Females (n = 87)	Males (n = 140)	P-value
Age (years)	72.0 (72.0–79.0)	66.5 (57.3–76.8)	**0.013**
Body height (m)	1.64 ± 0.08	1.77 ± 0.08	<**0.001**
Body weight (kg)	69.0 (62.0–80.0)	84.0 (73.0–95.0)	<**0.001**
BMI (kg/m^2)	26.3 (22.9–28.7)	26.5 (24.1–29.4)	0.546
Comorbidities			
Heart failure	16 (18.4%)	35 (25.0%)	0.246
Arterial hypertension	65 (74.7%)	93 (66.4%)	0.187
Coronary artery disease	23 (26.4%)	49 (35.0%)	0.178
Diabetes mellitus	20 (23.0%)	23 (16.4%)	0.220
History of stroke or TIA	10 (11.5%)	18 (12.9%)	0.761
History of myocardial infarction	8 (9.2%)	14 (10.0%)	1.000
Peripheral artery disease	12 (13.8%)	19 (13.6%)	0.761
History of venous thromboembolism	12 (13.8%)	7 (5.0%)	**0.026**
History of pulmonary embolism	5 (5.7%)	5 (3.6%)	0.512
History of deep venous thrombosis	12 (13.8%)	6 (4.3%)	**0.020**
Atrial fibrillation	48 (55.8%)	67 (50.4%)	0.431
CHA_2DS_2-VASc-Score (points)	4 (3–5)	2 (1–4)	0.102
Echocardiographic parameters			
Thrombus or spontaneous echo contrast	9 (11.7%)	7 (6.3%)	0.197
Thrombus without spontaneous echo contrast	4 (5.2%)	0 (0.0%)	**0.026**
Left ventricle ejection fraction	55.0% (50.0–55.0)	55.0% (37.5–55.0)	0.103
Left atrial longitudinal diameter (cm)	6.2 (5.5–6.9)	5.9 (5.3–6.6)	0.223
Left atrial septal-lateral diameter (cm)	4.2 (3.9–4.8)	4.3 (3.8–4.7)	0.787
Left atrial area (cm^2)	22.2 ± 6.6	21.6 ± 6.8	0.613
Right atrial septal-lateral diameter (cm)	3.8 ± 0.9	4.1 ± 0.8	0.642
Right atrial longitudinal diameter (cm)	5.3 (4.8–5.9)	5.4 (4.9–6.1)	0.190
Right atrial area (cm^2)	15.8 (12.7–19.8)	18.1 (15.0–22.9)	**0.024**
Systolic pulmonary artery pressure (mmHg)	39.1 ± 9.3	38.9 ± 11.5	0.907
Blood flow velocity in the LAA detected by Pulsed-waved Doppler (cm*sec^{-1})	41.2 (29.2–58.5)	50.0 (34.3–67.1)	**0.038**
LAA width (septal-lateral diameter) (cm)	1.8 (1.2–2.1)	1.7 (1.4–2.0)	0.455
LAA longitudinal diameter from aperture to apex (cm)	3.3 ± 0.8	3.3 ± 0.7	0.512

Abbreviations: LAA indicates left atrial appendage; BMI — Body mass index; TIA — transient ischemic attack.
P values of <0.05 (two-sided) were considered to be statistically significant.

in our study.[16,35] Incidence in men was in the nationwide sample of Germany 9.4% higher than in women. The higher incidence in males could be observed for all age-decades as described before.[35] In addition our study confirmed, that the incidence of ischemic stroke inclined relevantly with growing age in both genders.[1,7,10–13,27] Traditional risk factors for ischemic stroke comprise arterial hypertension, type II diabetes, hyperlipidemia, AF, smoking, overweight/obesity and other entities of metabolic syndrome as well as coronary artery disease.[36] In general these cardiovascular risk factors are present at a later age in women than in men, explaining a higher age in female stroke patients compared to males.[36,37] Diabetes mellitus, previous myocardial infarction and peripheral artery disease were more often found in male stroke patients, whereas women more frequently suffered from arterial hypertension and obesity.[38] AF and smoking were equally frequent in both genders.[38] The use of oral contraceptives, higher number of pregnancies and peri-as well as the post-menopausal periods might account for the increased stroke risk.[36]

Case-fatality rate after ischemic stroke

Our study results demonstrated a higher case-fatality rate in women compared to men after ischemic stroke events, which is in accordance with most reported studies.[26,35] The in-hospital mortality for women was 1.2-fold higher related to men. The most suggestive explanation for this higher in-hospital mortality rate is a higher burden of ischemic stroke in later life of females compared to males (Fig. 3), while the age-dependent mortality rate inclined parallel in both genders (Fig. 4B). Beside this effect on the in-hospital mortality, studies about stroke survivors showed in addition a more favourable outcome in men with better rehabilitation results.[26,36,37]

Although current guidelines recommend equal diagnostic and treatment strategies for stroke prevention in both genders, previously published studies have reported gender-differences.[26,36] A lower rate of imaging diagnostic procedures, carotid surgery antiplatelet agent treatment and - in some studies - additionally thrombolytic treatment is reported.[22,25–28,36] These factors may contribute to a less favourable outcome in females.

Table 2 Univariate regression analyses for the associations between several parameters and intra-cardiac thrombus formation (comprising solid thrombi and spontaneous echo contrast).

Variable	Females (n = 87)		Males (n = 140)	
	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
Age (per year)	1.054 (0.979–1.135)	0.161	1.064 (0.981–1.154)	0.136
Blood flow velocity in the LAA detected by Pulsed-waved Doppler (cm*sec^{-1})	**0.904 (0.837–0.976)**	**0.010**	0.953 (0.913–1.001)	0.053
LAA longitudinal diameter (cm)	**2.587 (1.070–6.253)**	**0.035**	**8.477 (1.849–38.861)**	**0.006**
LAA septal-lateral diameter (cm)	4.028 (0.999–16.250)	0.50	2.464 (0.910–6.673)	0.076
Left ventricle ejection fraction (%)	1.017 (0.933–1.110)	0.699	0.955 (0.894–1.019)	0.165
Right atrial septal-lateral diameter (cm)	0.903 (0.247–3.297)	0.878	**3.484 (1.091–11.128)**	**0.035**
Right atrial longitudinal diameter (cm)	1.001 (0.682–1.467)	0.997	1.012 (0.857–1.195)	0.889
Right atrial area (cm^2)	1.112 (0.895–1.380)	0.339	**1.200 (1.043–1.380)**	**0.011**
Left atrial septal-lateral diameter (cm)	0.638 (0.121–3.362)	0.596	**4.728 (1.360–16.432)**	**0.015**
Left atrial longitudinal diameter (cm)	0.851 (0.383–1.891)	0.691	2.801 (0.974–8.060)	0.056
Left atrial area (cm^2)	0.979 (0.800–1.198)	0.835	**1.245 (1.049–1.478)**	**0.012**
Systolic pulmonary artery pressure (mmHg)	0.989 (0.886–1.104)	0.842	1.004 (0.921–1.095)	0.923
BMI (kg/m^2)	1.028 (0.924–1.144)	0.610	0.909 (0.725–1.139)	0.407
Presence of Atrial Fibrillation	3.014 (0.583–15.587)	0.188	Regression was not calculable, therefore Chi–Quadrat test was used for calculation	**0.016**
History of venous thromboembolism	0.725 (0.082–6.442)	0.773	Regression was not calculable, therefore Chi–Quadrat test was used for calculation	1.000
Heart failure	**4.640 (1.060–20.305)**	**0.042**	4.754 (0.992–22.775)	0.051
Arterial Hypertension	1.357 (0.258–7.126)	0.718	3.000 (0.348–25.898)	0.318
Coronary artery disease	3.750 (0.902–15.588)	0.069	0.800 (0.148–4.332)	0.796
Diabetes mellitus	2.600 (0.623–10.856)	0.190	**5.308 (1.066–26.438)**	**0.042**
History of stroke or TIA	2.490 (0.430–14.405)	0.308	3.418 (0.591–19.764)	0.170
Peripheral artery disease	3.750 (0.780–18.025)	0.099	2.831 (0.497–16.122)	0.241
History of myocardial infarction	1.292 (0.137–12.150)	0.823	3.418 (0.591–19.764)	0.170
CHA_2DS_2-VASc-Score (points)	**1.629 (1.072–2.477)**	**0.022**	**1.701 (1.091–2.652)**	**0.019**

Abbreviations: LAA indicates left atrial appendage; BMI – Body mass index; TIA – transient ischemic attack.
P values of <0.05 (two-sided) were considered to be statistically significant.

Cardio-embolic stroke and promoting factors of atrial thrombi

Interestingly, AF was more frequently detected in female stroke patients compared to males in the German nationwide sample. This may be attributed to a later peak in life of ischemic stroke in women compared to men (Fig. 3), as the incidence of AF inclines with growing age in both genders.[39] Also Fang et al.[40] reported a higher AF-related thromboembolism leading to ischemic strokes in women compared to men.[40] In general, patients with AF have a 3- to 5-fold elevated relative risk for occurrence of stroke in comparison to individuals without.[3,30] Cardio-embolic stroke events account for about one fifth of the ischemic stroke events.[29] Thromboembolic strokes due to AF are often devastating, resulting in severe impairment or death in the majority of patients.[29,31,32]

For cardio-embolic stroke, the left atrial appendage (LAA) plays the most important role due to the fact that LAA harbors approximately 90% of intra-cardiac thrombi in AF.[13] Supporting previously published study results, lower blood flow velocity in the LAA[41,42] as well as larger LAA dimensions[43] were accompanied with atrial thrombi development. As expected, a higher CHA_2DS_2.VASc-score and presence of heart failure both promoted atrial thrombi in both genders.

Surprisingly, AF, diabetes, larger left and right atrial septal-lateral diameters and areas were associated with atrial thrombi in male patients, but not in females, which might be driven by the gender-difference in solid thrombi in our study. However, these results have to be interpreted with great caution, particularly in the view of fact that our single-center study cohort sample is only of medium size. It is well established, that female gender is one of the risk factors (in co-prevalence with other cofactors) for higher thromboembolic burden in AF patients and therefore was included in the CHA_2DS_2-VASc-Score.[33] However, some gender-differences in cardio-embolic stroke are well recorded such as the fact that underlying valvular disease is more common in female, whereas more men with this condition suffer from coronary artery disease.[44] In general, AF, recent myocardial infarction, the presence of mechanical prosthetic valves, dilated myocardiopathy and mitral rheumatic stenosis are conditions connected with a highly elevated risk for a cardio-embolic stroke.[45]

Table 3 Prognostic performance for prediction of thrombus formation (comprising solid thrombus and spontaneous echo contrast).

Parameter	Gender	P-value	Area under the curve (95% CI)	Calculated cut-off value	Sensitivity	Specificity	Positive predictive value	Negative predictive value
CHA_2DS_2Vasc-score (points)	Female	**0.039**	0.712 (0.542—0.883)	**5.5 points**	0.444	0.853	0.286	0.921
	Male	**0.049**	0.722 (0.545—0.900)	**4.5 points**	0.571	0.095	0.040	0.769
LAA longitudinal diameter (cm)	Female	**0.040**	0.713 (0.535—0.891)	**3.90 cm**	0.556	0.817	0.313	0.925
	Male	**0.005**	0.817 (0.654—0.981)	**3.95 cm**	0.714	0.859	0.263	0.977
Right atrial area (cm^2)	Female	0.567	0.600 (0.217—0.983)	**18.95 cm^2**	0.667	0.650	0.125	0.963
	Male	**0.028**	0.795 (0.566—1.000)	**22.50 cm^2**	0.800	0.772	0.211	0.981
Left atrial area (cm^2)	Female	0.965	0.493 (0.157—0.830)	**23.15 cm^2**	0.500	0.730	0.167	0.931
	Male	**0.011**	0.842 (0.715—0.970)	**24.10 cm^2**	1.000	0.667	0.185	1.000

Abbreviations: LAA indicates left atrial appendage.
P values of <0.05 (two-sided) were considered to be statistically significant.

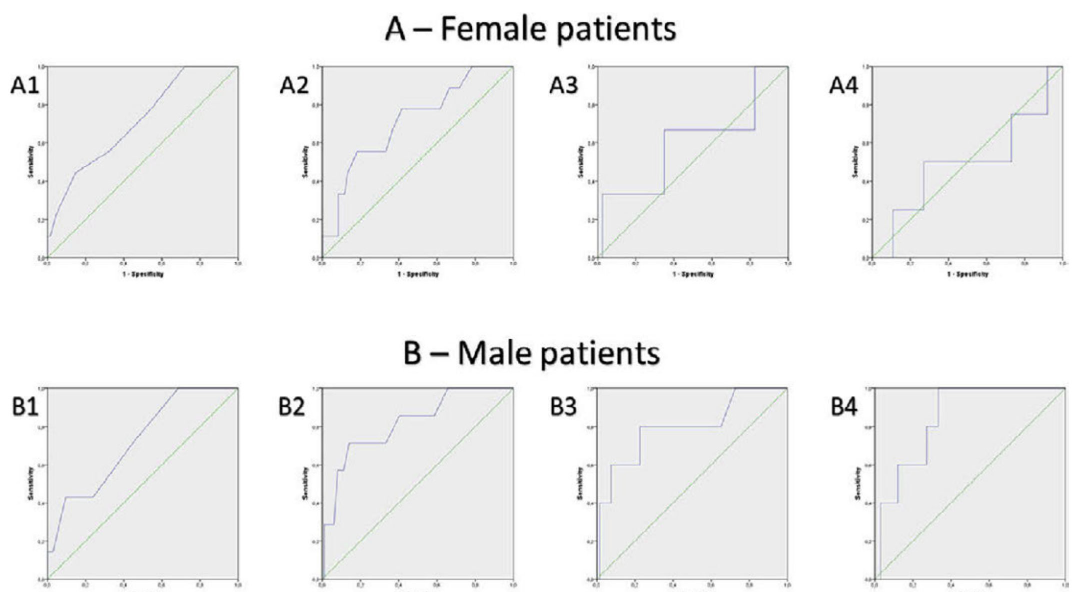

Figure 6 ROC curves for prediction of thrombus formation (comprising solid thrombus and spontaneous echo contrast) by several parameters in female (A) and male (B) patients: A1 and B1: CHA_2DS_2Vasc-score, A2 and B2: Left atrial appendage longitudinal diameter, A3 and B3: Right atrial area, A4 and B4: Left atrial area.

But beyond thrombi development in AF, a growing body of evidence indicates that additionally the LA size has been determined to be a predictor of stroke and death in the general population and an increased LA volume is predictive for the onset of first stroke in elderly individuals who are in sinus rhythm and do not have a history of ischemic neurologic events, AF, or valvular heart disease.[46] Therefore, it might be hypothetically, whether a larger LA volume[47] and larger LAA sizes[48] per se may attribute to atrial thrombi development in men in absence of AF, especially in combination with a decreased blood flow velocity. This may one possible explanation regarding the gender-differences in atrial thrombi development.

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 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.

Limitations

Our study has some limitations. The data of the nationwide sample from Federal Statistical Office of Germany (Statistisches Bundesamt, DEStatis) for this analysis are pooled/aggregated data. Therefore, we can only present a descriptive data analysis, without statistical testing for difference with P-values and without adjustment for age and other cofactors such as comorbidities (e.g. cardiovascular disease). Furthermore, only patients treated in-hospital were included. In addition, antithrombotic regimes was not reported, thus its influence remains unclear.

The central limitations of the second study-part are the single-center design and the retrospective data assessment of a medium sized patient cohort. Follow-up examinations are missing. In addition, only a small number of *solid* thrombi could be detected in the patient cohort, not allowing for statistically significant evidence. Thus, we decided to analyse solid thrombi and SEC as equivalent for atrial thrombi.[13] The occurrence of SEC was assessed by at least two experienced echocardiographers.

Despite of these limitations, we were able to identify important gender-specific differences in ischemic stroke.

Notes

Funding

This study was supported by the German Federal Ministry of Education and Research (BMBF 01EO1003 and BMBF 01EO1503). The authors are responsible for the contents of this publication.

Potential conflicts of interests

None.

Acknowledgements

We thank the Federal Statistical Office of Germany (Statistisches Bundesamt, DEStatis) for providing the data/results and the kind permission to publish these data/results.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.artres.2018.05.004.

References

1. Soler EP, Ruiz VC. Epidemiology and risk factors of cerebral ischemia and ischemic heart diseases: similarities and differences. *Curr Cardiol Rev* 2010;**6**:138—49.
2. Johnson W, Onuma O, Owolabi M, Sachdev S. Stroke: a global response is needed. *Bull World Health Org* 2016;**94**:634—634A.
3. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Europace* 2016;**18**:1609—78.
4. Sanna T, Diener HC, Passman RS, Di Lazzaro V, Bernstein RA, Morillo CA, et al. Cryptogenic stroke and underlying atrial fibrillation. *N Engl J Med* 2014;**370**:2478—86.
5. Dobkin BH. Clinical practice. Rehabilitation after stroke. *N Engl J Med* 2005;**352**:1677—84.
6. Furie KL, Kasner SE, Adams RJ, Albers GW, Bush RL, Fagan SC, et al. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the american heart association/american stroke association. *Stroke* 2011;**42**:227—76.
7. Feigin VL, Forouzanfar MH, Krishnamurthi R, Mensah GA, Connor M, Bennett DA, et al. Global burden of diseases I, risk factors S and the GBDSEG. Global and regional burden of stroke during 1990-2010: findings from the global burden of disease study 2010. *Lancet* 2014;**383**:245—54.
8. Kapral MK, Fang J, Hill MD, Silver F, Richards J, Jaigobin C, et al. Sex differences in stroke care and outcomes: results from the Registry of the Canadian Stroke Network. *Stroke* 2005;**36**:809—14.
9. Lee S, Shafe AC, Cowie MR. UK stroke incidence, mortality and cardiovascular risk management 1999-2008: time-trend analysis from the General Practice Research Database. *BMJ Open* 2011;**1**:e000269.
10. Bonita R. Epidemiology of stroke. *Lancet* 1992;**339**:342—4.
11. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 1991;**22**:983—8.
12. Zhang Y, Chapman AM, Plested M, Jackson D, Purroy F. The incidence, prevalence, and mortality of stroke in France, Germany, Italy, Spain, the UK, and the US: a literature review. *Stroke Res Treat* 2012;**2012**:436125.
13. Fuller CJ, Reisman M. Stroke prevention in atrial fibrillation: atrial appendage closure. *Curr Cardiol Rep* 2011;**13**:159—66.
14. Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J* 2013;**34**:2949—3003.
15. Schmidt M, Jacobsen JB, Lash TL, Botker HE, Sorensen HT. 25 year trends in first time hospitalisation for acute myocardial infarction, subsequent short and long term mortality, and the prognostic impact of sex and comorbidity: a Danish nationwide cohort study. *BMJ* 2012;**344**:e356.
16. Appelros P, Stegmayr B, Terent A. Sex differences in stroke epidemiology: a systematic review. *Stroke* 2009;**40**:1082—90.
17. Milcent C, Dormont B, Durand-Zaleski I, Steg PG. Gender differences in hospital mortality and use of percutaneous coronary intervention in acute myocardial infarction: microsimulation analysis of the 1999 nationwide French hospitals database. *Circulation* 2007;**115**:833—9.
18. Maas AH, van der Schouw YT, Regitz-Zagrosek V, Swahn E, Appelman YE, Pasterkamp G, et al. Red alert for women's heart: the urgent need for more research and knowledge on cardiovascular disease in women: proceedings of the workshop held in Brussels on gender differences in cardiovascular disease, 29 September 2010. *Eur Heart J* 2011;**32**:1362—8.
19. Mosca L, Barrett-Connor E, Wenger NK. Sex/gender differences in cardiovascular disease prevention: what a difference a decade makes. *Circulation* 2011;**124**:2145—54.
20. Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M, et al. European association for cardiovascular P, rehabilitation and guidelines ESCCfP. European guidelines on cardiovascular disease prevention in clinical practice (version 2012). The fifth joint task force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts). *Eur Heart J* 2012;**33**:1635—701.
21. Kolominsky-Rabas PL, Weber M, Gefeller O, Neundoerfer B, Heuschmann PU. Epidemiology of ischemic stroke subtypes according to TOAST criteria: incidence, recurrence, and long-term survival in ischemic stroke subtypes: a population-based study. *Stroke* 2001;**32**:2735—40.
22. Di Carlo A, Lamassa M, Baldereschi M, Pracucci G, Basile AM, Wolfe CD, et al. Sex differences in the clinical presentation, resource use, and 3-month outcome of acute stroke in Europe: data from a multicenter multinational hospital-based registry. *Stroke* 2003;**34**:1114—9.
23. Kannel WB. The Framingham Study: historical insight on the impact of cardiovascular risk factors in men versus women. *J Gend Specif Med* 2002;**5**:27—37.
24. Canto JG, Rogers WJ, Goldberg RJ, Peterson ED, Wenger NK, Vaccarino V, et al. Association of age and sex with myocardial infarction symptom presentation and in-hospital mortality. *J Am Med Assoc* 2012;**307**:813—22.

25. Reeves MJ, Bushnell CD, Howard G, Gargano JW, Duncan PW, Lynch G, et al. Sex differences in stroke: epidemiology, clinical presentation, medical care, and outcomes. *Lancet Neurol* 2008;**7**:915—26.
26. Glader EL, Stegmayr B, Norrving B, Terent A, Hulter-Asberg K, Wester PO, et al. Sex differences in management and outcome after stroke: a Swedish national perspective. *Stroke* 2003;**34**:1970—5.
27. Kessler C, Khaw AV, Nabavi DG, Glahn J, Grond M, Busse O. Standardized prehospital treatment of stroke. *Dtsch Arztebl Int* 2011;**108**:585—91.
28. Stewart S, Hart CL, Hole DJ, McMurray JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. *Am J Med* 2002;**113**:359—64.
29. Ferro JM. Cardioembolic stroke: an update. *Lancet Neurol* 2003;**2**:177—88.
30. Kamel H, Okin PM, Elkind MS, Iadecola C. Atrial fibrillation and mechanisms of stroke: time for a new model. *Stroke* 2016;**47**:895—900.
31. Gladstone DJ, Spring M, Dorian P, Panzov V, Thorpe KE, Hall J, et al. Atrial fibrillation in patients with cryptogenic stroke. *N Engl J Med* 2014;**370**:2467—77.
32. Steger C, Pratter A, Martinek-Bregel M, Avanzini M, Valentin A, Slany J, et al. Stroke patients with atrial fibrillation have a worse prognosis than patients without: data from the Austrian Stroke registry. *Eur Heart J* 2004;**25**:1734—40.
33. Olesen JB, Lip GY, Hansen ML, Hansen PR, Tolstrup JS, Lindhardsen J, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. *BMJ* 2011;**342**:d124.
34. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the american Society of echocardiography and the European association of cardiovascular imaging. *Eur Heart J Cardiovasc Imaging* 2015;**16**:233—70.
35. Wyller TB. Stroke and gender. *J Gend Specif Med* 1999;**2**:41—5.
36. Haast RA, Gustafson DR, Kiliaan AJ. Sex differences in stroke. *J Cerebr Blood Flow Metabol* 2012;**32**:2100—7.
37. Petrea RE, Beiser AS, Seshadri S, Kelly-Hayes M, Kase CS, Wolf PA. Gender differences in stroke incidence and poststroke disability in the Framingham heart study. *Stroke* 2009;**40**:1032—7.
38. Andersen KK, Andersen ZJ, Olsen TS. Age- and gender-specific prevalence of cardiovascular risk factors in 40,102 patients with first-ever ischemic stroke: a Nationwide Danish Study. *Stroke* 2010;**41**:2768—74.
39. Zoni-Berisso M, Lercari F, Carazza T, Domenicucci S. Epidemiology of atrial fibrillation: European perspective. *Clin Epidemiol* 2014;**6**:213—20.
40. Fang MC, Singer DE, Chang Y, Hylek EM, Henault LE, Jensvold NG, et al. Gender differences in the risk of ischemic stroke and peripheral embolism in atrial fibrillation: the AnTicoagulation and Risk factors in Atrial fibrillation (ATRIA) study. *Circulation* 2005;**112**:1687—91.
41. Fatkin D, Kelly RP, Feneley MP. Relations between left atrial appendage blood flow velocity, spontaneous echocardiographic contrast and thromboembolic risk in vivo. *J Am Coll Cardiol* 1994;**23**:961—9.
42. Takashima S, Nakagawa K, Hirai T, Dougu N, Taguchi Y, Sasahara E, et al. Transesophageal echocardiographic findings are independent and relevant predictors of ischemic stroke in patients with nonvalvular atrial fibrillation. *J Clin Neurol* 2012;**8**:170—6.
43. Beinart R, Heist EK, Newell JB, Holmvang G, Ruskin JN, Mansour M. Left atrial appendage dimensions predict the risk of stroke/TIA in patients with atrial fibrillation. *J Cardiovasc Electrophysiol* 2011;**22**:10—5.
44. Michelena HI, Ezekowitz MD. Atrial fibrillation: are there gender differences? *J Gend Specif Med* 2000;**3**:44—9.
45. Arboix A, Alio J. Cardioembolic stroke: clinical features, specific cardiac disorders and prognosis. *Curr Cardiol Rev* 2010;**6**:150—61.
46. Abhayaratna WP, Seward JB, Appleton CP, Douglas PS, Oh JK, Tajik AJ, et al. Left atrial size: physiologic determinants and clinical applications. *J Am Coll Cardiol* 2006;**47**:2357—63.
47. D'Andrea A, Riegler L, Rucco MA, Cocchia R, Scarafile R, Salerno G, et al. Left atrial volume index in healthy subjects: clinical and echocardiographic correlates. *Echocardiography* 2013;**30**:1001—7.
48. Li CY, Gao BL, Liu XW, Fan QY, Zhang XJ, Liu GC, et al. Quantitative evaluation of the substantially variable morphology and function of the left atrial appendage and its relation with adjacent Structures. *PLoS One* 2015;**10**:e0126818.