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Title: Demographics, treatment and outcomes of atrial fibrillation in a developing country: the population-based TuRkish Atrial Fibrillation (TRAF) cohort

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Abstract

Aims: Although atrial fibrillation (AF) is increasingly common in developed countries, there is limited knowledge regarding its demographics, precursors, treatments and outcomes among developing countries. We present the profile of the TuRkish Atrial Fibrillation (TRAF) cohort which provides information about prevalence, incidence, co-morbidities, treatment, healthcare utilisation and outcomes associated with AF in Turkey.

Methods and results: The TRAF cohort was established from MEDULA, a health insurance database linking hospitals, general practitioners, pharmacies and outpatient clinics for almost 100% of the 50,364,653 inhabitants of Turkey. The cohort includes 542,130 individuals with AF between 2008 and 2012 aged >18 years who survived the first 30 days following diagnosis. Of 402,674 (54.6% female, 74.8% non-valvular and 25.2% valvular) individuals with AF, in 2012 the incidence of non-valvular AF (0.17%) was higher than valvular AF (0.04%). Overall, the frequencies of co-morbidities for non-valvular and valular AF were: hypertension 82.8 vs. 90.4%; heart failure 48.6 vs. 69.0%; COPD 36.3 vs. 39.9%; diabetes mellitus 24.4 vs. 23.7% and acute myocardial infarction 11.1 vs 12.4%. Hospitalisation rates following AF were lower for non-valvular (7.6%) than valvular (15.1%) AF. Warfarin was prescribed to 39.X% of individuals with a CHADS2-VASc ≥2. At X-years, rates of ischaemic stoke and all-cause mortality were XX.X% and YY.Y%, respectively.

Conclusion: The TRAF cohort is the first population-based, whole-country cohort of AF epidemiology, quality of care and outcomes. It will provide a unique opportunity to study the patterns, causes and impact of treatments on the incidence and outcomes of AF in a developing country.

Keywords: Atrial fibrillation, incidence, prevalence, risk, aetiology, stroke, death, warfarin, population-based cohort

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. It conveys a substantial international health and wealth burden, which is mostly driven by high rates of stroke, thromboembolism and death (1). Moreover, the prevalence and incidence of AF is increasing, especially among developed countries with an elderly population (2). Although the epidemiology of AF has been extensively reported in modern healthcare systems, there are no qualified data about the demographics, risk factors, treatments and outcomes among developing countries. Typically, these counties have younger populations and rapidly embrace new health technologies. In addition, most of the randomised data that are used to report the epidemiological features of AF have, to date, only included a limited number of patients living in finite areas. There are no population-based or whole-country studies of the life course of patients with AF from aetiology to treatment to healthcare utlisation, morbidity and death.

We have established the first whole-country cohort of individual patient data from a systematic health insurance database which covers nearly all 50,364,653 inhabitants of Turkey. The overall aim of the TuRkish Atrial Fibrillation (TRAF) cohort is to further clinical knowledge about the real world prevalence, incidence, demographics, co-morbidities, treatments, quality of care and outcomes for all types of AF. Here, we present the overall design and methods of the TRAF cohort, the age- and sex-specific prevalence and incidence of AF, as well as data for prescribed drugs, co-morbidities and observed clinical events including stroke, systemic embolism, major bleeding, hospitalisations and mortality.

Methods

Data Source

Data for the TRAF cohort were obtained from the Turkish claims and utilisation management system, MEDULA, which processes claims for all health insurance funds in Turkey. Covering close to 100 % of the population, MEDULA is comprised of pharmacy, inpatient, outpatient and laboratory claims and across 23,500 pharmacies, 20,000 general practitioners, 850 government hospitals, 60 university hospitals and 500 private hospitals. Medical data are entered into the MEDULLA database by physicians, which includes patient demographics, prescription details, observed clinical events, outpatient clinics, inpatient hospitalisations and major clinical outcomes. For each hospitalisation, the dates of admission and discharge, main diagnoses and major outcomes are recorded. The MEDULLA system links to the Turkish national death database, whereby information concerning date and cause of death are available. The TRAF cohort is formed from extracted anonymised patient-level data.

Study population

We included all individuals with a diagnosis of AF who were aged over 18 years between January 1st, 2008 and December 31st, 2012 and who survived the first 30 days following their diagnosis of AF. We excluded those patients who died very early after a diagnosis of AF because…… We used ICD-10 code I48 to identify AF. We defined patients as having non-valvular AF according to international guidelines by excluding those who had mitral stenosis (I342, I050, Q232) or a history of valve surgery (ICD codes XXXXXXXXX). We defined lone AF as those patients with non-valvular AF who had no co-morbidity.

Co-morbidity data

Co-morbidity data such as hypertension (I10–15), heart failure (I50), chronic obstructive airways disease, COPD (J43-44), peripheral vascular disease (I70–73), diabetes mellitus (E10-14) and acute myocardial infarction (I21, I25.2), hyperthyroidism (E05), renal disease (N17-19), and outcomes data including thromboembolic (ischaemic stroke (I63), non-specified stroke (I64), transient ischaemic attack, TIA (G45) systemic emboli (I74)) and major haemorrhagic

(haemorrhagic stroke (ICD xxx), others….) events were extracted. The ICD-10 codes used for the diagnostic categories can be seen in Supplementary table 1.

Prescribed medications data

We used the ATC/DDD Index of drug codes to identify prescribed medications (4). Extracted medications data included that for warfarin (B01AA03), acetyl salicylic acid (aspirin) (B01AC06), clopidogrel (B01AC04), β blockers (C07), verapamil (C08DA01), diltiazem (C08DB01), amiodarone (C01BD01), sotalol (C07AA07) and propafenone (C01BC03). During the study period, warfarin was the only oral anticoagulant available for AF.

Healthcare utlisation and outcomes data

We extracted from the MEDULLA database dates of hospital admissions and discharges along with the reason for hospitalisation.

Stroke risk schemes

We extracted patient-level information to enable the calculation of the CHADS2 and CHA2DS2VASc stoke risk schemes for AF. The components of the CHADS2 score were defined by a diagnosis of heart failure, hypertension, age at inclusion, diabetes mellitus and previous ischemic stroke, unspecified stroke, TIA, or systemic emboli. Components of the CHA2DS2VASc score were, in addition to the factors used for definition of the CHADS2 score, vascular disease (prior acute myocardial infarction, peripheral arterial disease and sex) (3).

Statistical analysis

The distribution of continuous variables was determined using the Kolmogorov-Smirnov test. Continuous variables with normal distribution were expressed as means ± standard deviations (SD). Variables with skew distributions were expressed as median (minimum-maximum) and categorical variables expressed as proportions.

Categorical variables were compared using the Chi-squared test, normally distributed numeric variables compared using the independent samples Students t test, and skewed numeric variables compared using the Mann Whitney U test. Pearson or age- and sex- standardised rates of the incidence of AF were calculated by…..

Spearman's correlation, where appropriate, was used to explore the associations between study parameters. Generalised ordinal logistic regression models were used to quantify the impact of independent risk factors for AF. Two-sided values of $P<0.05$ were considered statistically significant. All analyses were performed using SPSS 15.0, R, and STATA 8.0 software.

Results

Between 2008 and 2012, the estimated prevalence of AF in turkey was 1.08%, 95% Cı x.xx to x.xx%) Of 542,130 subjects between 2008 and 2012, aged over 18 years who had a diagnosis of AF and survived the first 30 days after index date, there were 402,674 (74.8 %) with non-valvular AF and 139,456 (25.2 %) with valvular AF. Of those with non-valvular AF, XXXXX (5.8%) had lone AF.

Overall, there were XXXXXXXX person-years of follow-up over a median (interquartile range) of xx (xx to xx) months. For this cohort, mean (SD) age xx.x (xx.x) years, xx.x% female, there were xxxxx (xx.x%) deaths, xxxxx (xx.x%) ischaemic strokes, xxxx major haemorrhages and xxxxxxx days of hospital stay. Table 1 shows the baseline clinical characteristic of the overall cohort and split by AF category.

The median (minimum-maximum) CHA2DS2-VASc and CHA2DS2 scores were 4 (0-9) and 2 (0-6), respectively (Figure 5). In total XXXXXX (XX.X%) of individuals with AF were eligible for an oral anticoagulant (assuming no contraindications) according to either a CHADS score ≥2 (39.X%) or a CHA2DS2-VASc score ≥2 (XX.X%).

Overall, 32.1% of individuals with a CHA2DS2-VASc score of 0 and 35% with CHA2DS2-VASc score of 1 were prescribed warfarin while only 39% with a CHA2DS2-VASc score ≥ 2 warfarin prescription.

Non-valvular AF

For individuals with non-valvular AF (mean (SD) age xx (xx) years, 54.6% female), the prevalence was 0.80% and, in 2012, the incidence was 0.17%. The prevalence of non-valvular AF increased with increasing age; being 0.06% for ages 19-29 years, 0.11% for ages 30-39 years, 0.27% for ages 40-49 years, 0.77 % for ages 50-59 years, 2.13% for ages 60-69 years, 4.94% for ages 70-79 years, 6.21% for ages 80-89 years and 6.68% ages over 90 years (Figure 1). insert sex-standardised rates here.

Among this group, the frequencies of co-morbidities were: hypertension 82.8%, heart failure 48.6%, COPD 36.3%, diabetes mellitus 24.4% and acute myocardial infarction 11.1% (Figure 2). The x-year hospitalisation rate following the diagnosis was 7.6%. A total of 25,324 (6.3%) patients had an ischemic stroke after their diagnosis of non-valvular AF. All-cause mortality at x years after diagnosis of non-valvular AF was 21.1% (85,204 individuals).

Valvular AF

For subjects with valvular AF (mean (SD) age xx (xx)x years, 65.1% women), the prevalence 0.28% and, in 2012, the incidence was 0.04%. The prevalence of valvular AF also increased by age; being 0.01% for ages 19-29 years, 0.04% for ages 30-39 years, 0.14% for ages 40-49 years, 0.38% for ages 50-59 years, 0.84% for ages 60-69 years, 1.44% for ages 70-79 years, 1.22% for ages 80-89 years, and 0.73% over the age of 90 years (Figure 1). insert sex-standardised rates here.

Major co-morbidities for this group included hypertension (90.4%),heart failure (69.0%) , COPD (39.9%), diabetes mellitus (23.7%, and acute myocardial infarction (12.4%) (17324) of the patients with valvular AF (Figure 2). The x-year hospitalisation rate after diagnosis of valvular AF was 15.1%. A total of 10,122 patients (7.3%) had an ischemic stroke after their diagnosis valvular AF. All-cause mortality at x years after diagnosis of valvular AF was 16.2% (22,602 individuals).

Lone AF

Individuals with lone AF constituted the 5.8% of the group with non valvular AF. When we considered individuals with lone AF aged under 60 years, the frequency was 4.0 %. insert sex-standardised rates here. However, all-cause mortality at 5-year follow-up was 16.7% across all ages and 3.3% among those under 60 years of age.

Discussion

Atrial fibrillation is a heterogeneous condition with significant differences in its epidemiology, pathogenesis, clinical presentation and management across the age groups. Most of the published data regarding the epidemiology and prognosis of atrial fibrillation arise from Northern America and the Western European countries. There are no total cohort studies of AF. Our population-based cohort of AF is the first-of-its-kind, as well as being unique because it comprises data from a developing country.

Data from the TRAF cohort, 2008-2012 suggest that the prevalence and the incidence of non-valvular AF in Turkey was lower than that reported in Western and modern healthcare systems. In the UK between 2009 and 2012, for example, an analysis of 13.1 million patients in primary care revealed a prevalence of AF of 1.76%. Our lower rate probably reflects the younger demographics of the Turkish population in concert, and a well recognized strongly positive association with increasing age. In Turkey the median age is 30.1 years and only 7.5 % of inhabitants of Turkey are over 65 years of age (5). This compares with a median age of 37.2 and 38.X years and 13.3% and 16.7% over the ages of 65 years in Northern America and Europe, respectively (6).

Although the prevalence of non-valvular AF was lower than that reported in the Western world, we found that the prevalence of valvular was high in Turkey. In Turkey, acute rheumatic fever and its complications, although significantly reduced, have not been eradicated. This is an important finding from our study which has

critical public health repercussion should Turkey wish to address preventable valvualar heart disease and associated valvular AF. Not withstanding this, the current figure of more than half a million patients with AF will result in a significant and increasing burden on health economy of Turkey. This burden will be driven by an aging and multimorbid population in coming years.

In the previous reports from the Western healthcare systems, the prevalence of AF is reported to be greater in men than women (1). In the TRAFT cohort, we found tevidence for the converseand contrast with the ATRIA study, Euro Heart Survey, and Framingham study (7-9). We believe that this is because…..

During the 5 year study period, warfarin was the only oral anticoagulant drug that was available in Turkey for stroke prevention in AF. Novel oral anticoagulants such as dabigatran, rivaroxaban and apixaban were not available at the time. We found that that warfarin was not used appropriately for patients with AF. About one third of low the risk group (CHA2DS2-VASc score of 0) were prescribed warfarin. Equally, only 39 X% of the high risk group (CHADS score ≥2 or CHA2DS2-VASc score ≥2) were prescribed warfarin. This inappropriate use of warfarin is likely to result in medical harm, and warrants further study in the TRAF cohort. Our work further highlights the importance of estimating stroke risk systematically across hospitals, in primary care and at other times of interaction with healthcare professionals – as well as acting upon the results. In the UK, the prescription of oral anticoagulants according to stroke risk has improved over time, but there remains evidence for a risk-treatment paradox. In part, UK quality improvements have been as a result of educational interventions, which could be templated and tested in developing countries.

Another important finding from the TRAF cohort was contemporary and population-based evidence for high mortality rates among patients with AF that occurred early following index diagnosis. In the literature AF is reported to confer a 5-fold risk of stroke and 2-fold risk of mortality(1). We found that the rate of death at x years was xx.x%. It is probably that this was related to the inappropriate use of oral anticoagulants because if all eligible high risk patients had received warfarin, then with a relative risk reduction of x.x, y deaths could have been prevented.

Even so, the increasing incidence and prevalence of AF will continue to impose a considerable burden on the Turkish medical health-care system (10-12). Whilst we found a well reported association between AF, increasing age, and concomitant diseases such as hypertension, coronary artery disease, and heart failure (13-15), dta from the TRAF cohort will help determine whether the excess mortality observed in patients with AF is directly due to AF or is just an association. That is, other large cohort-based studies have shown AF to be independent predictor of increased late mortality (16). Data from the Framingham study revealed a 1.5- to 1.9-fold risk of mortality in patients with AF in both gender across a wide range of ages even after adjustment for pre-existing cardiovascular disease (17). In another study, Wolf et al. (18) found that the adjusted relative risk of mortality was about 20% higher in patients with AF during 3 years of follow-up. There was no significant difference between age categories or genders during follow-up. In another study, Frost et al. (19) found a statistically significant difference in the relative risk of mortality between genders in age categories older than 70 years during 14 years of follow-up. Andersson et al. (12) reported an adjusted relative risk for all-cause mortality amongst patients with incident AF of 1.5 –2, with higher relative risks in younger individuals and females. In our study during 5 years follow up period mortality rate was 32.6%. This rate was about half in patients with AF who had no any other comorbidity.

The costs associated with AF patient care are high and are driven largely by the cost of hospitalisation. A number of real-world observational studies have demonstrated that patients with AF are frequently admitted or readmitted to hospital. In a study reported by Naccarelli et al.(20), more than half (51.9%) were hospitalized with nonfatal outcomes over a mean follow-up period of 24 months, and 38.3% were hospitalized during the first year. Wu et al.(21) reported nearly half of the patients with AF required 1 inpatient visit over 1 year compared to 6.6% of a matched non-AF sample. In the study of Naccarelli et al.(20), 27.2% of patients were hospitalized for CV causes over the 2 years of follow-up. In our study 31.5% of all patients with AF were hospitalized during follow-up period.

Conclusion

The TRAFT cohort, is the first total (whole country, all population) cohort of AF. It contains detailed information about incidence, prevalence, co-morbidities, treatments and outcomes. Our initial cohort analysis demonstrated that the prevalence of AF in Turkey was lower than other countries, but the incidence was strongly related to the age and multimorbidity. For Turkey, AF is therefore expected to increase with the ageing Turkish population. High mortality and morbidity rates associated with AF in Turkey are likely to be associated with a risk treatment paradox, that warrants evaluation such that avoidable deaths are reduced in light of the burgeoning AF population.

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TABLES

Table 1: ICD-10 codes

Diagnosis	ICD-10 code
Heart failure	I50
Hypertension	I10-15
Diabetes mellitus	E10-14
Ischemic stroke	I63
Stroke, unspecified	I64
TIA	G45
Peripheral systemic embolism	I74
Thromboembolic event	I63-64, G45, I74
Acute myocardial infarction	I21, I252
Ischemic heart disease	I20-25
Peripheral arterial disease	I70-73
Vascular disease	I21, I252, I65, I70-73
Valvular disease	I05-09, I33-39
Mitral stenosis	I342, I050, I052, Q232
Renal disease	N17-19 or local code for renal transplantation/dialysis
Chronic pulmonary disease	J40-70
Emphysema/COPD	J43-44
Hyperthyroidism	E05

Figures

Figure 1: Age distribution of non-valvular AF prevalence

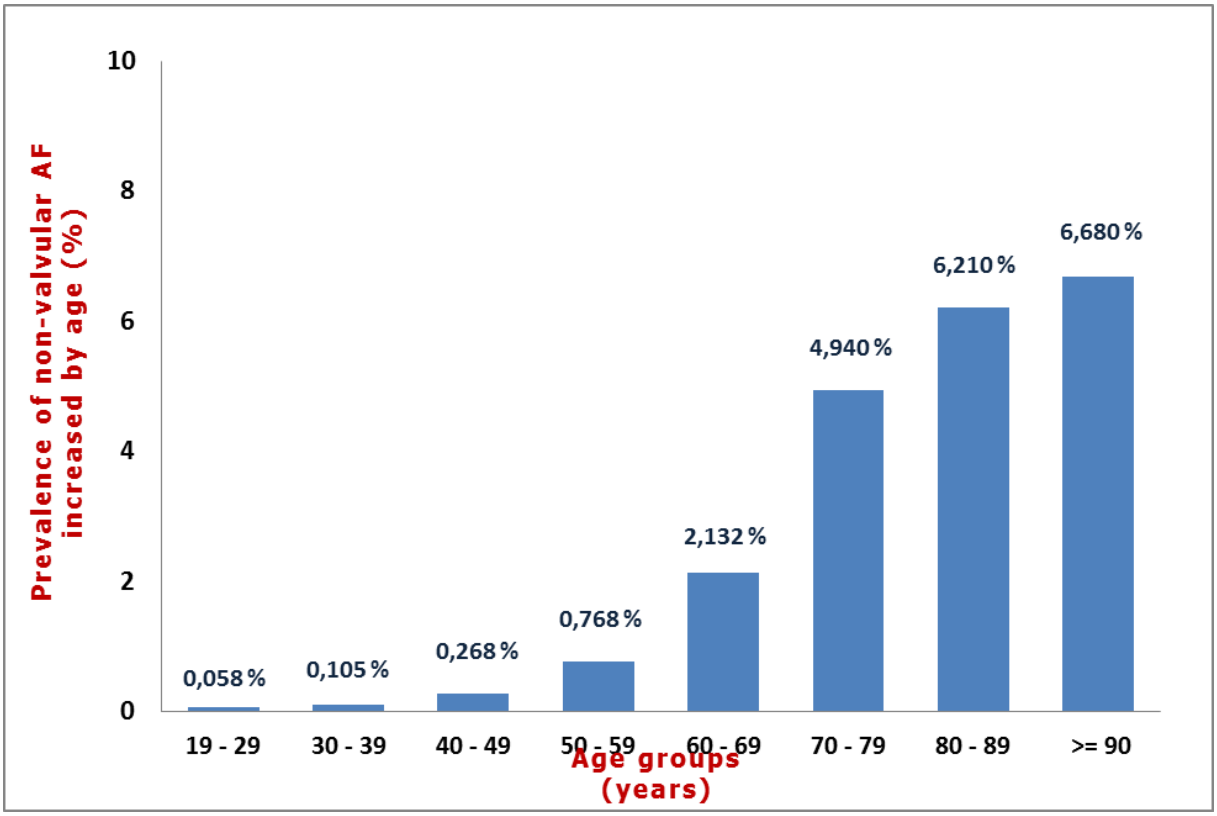

Figure 2: Comobidities in non-valvular AF

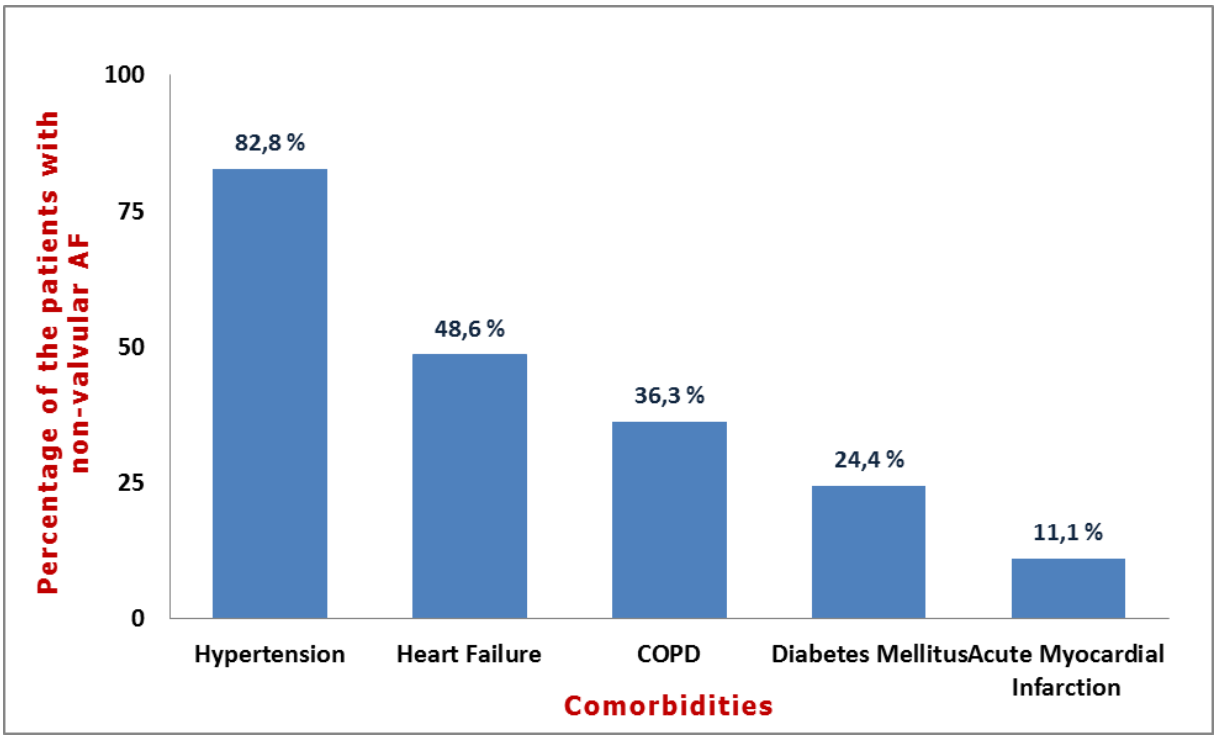

Figure 3: Age distribution of valvular AF prevalence

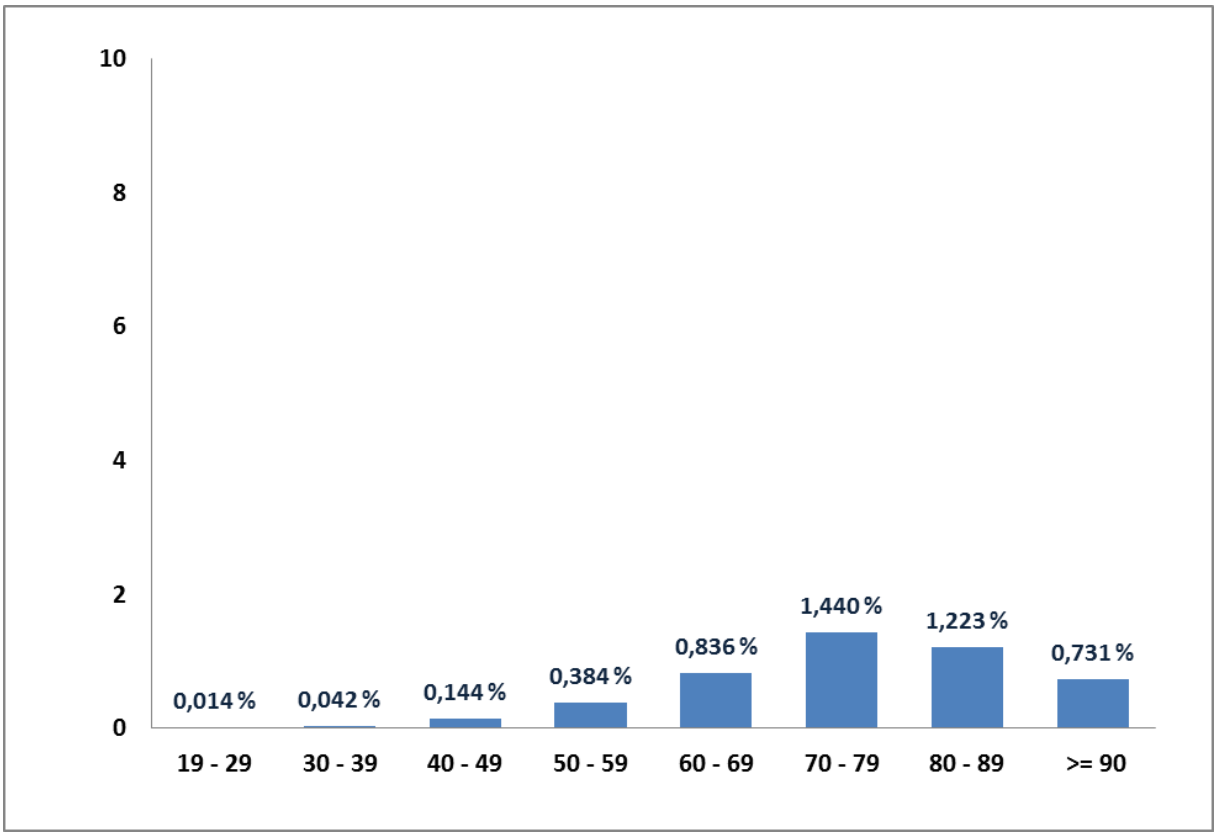

Figure 4: Comobidities in valvular AF

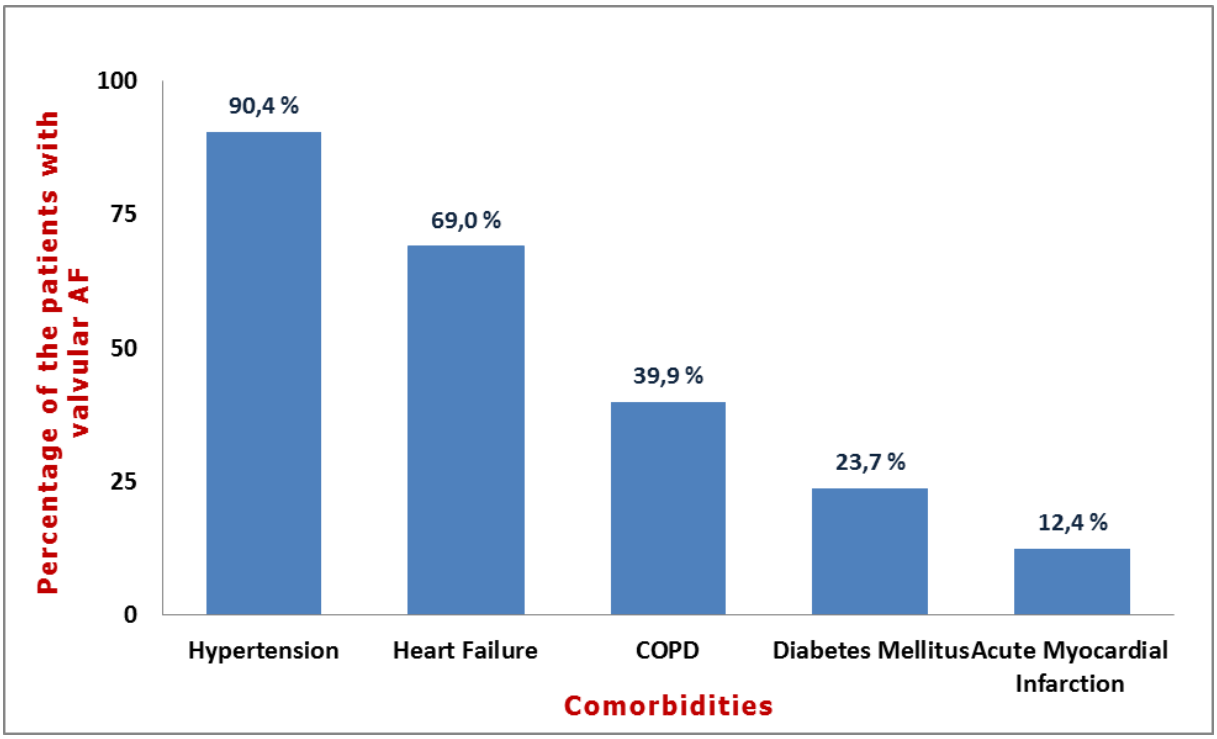

Figure 5: The distributions of risk scores for stroke (CHADS2 and CHADS2Vasc)