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

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

Methods and results The TRAF cohort was extracted from MEDULA, a health insurance database linking hospitals, general practitioners, pharmacies and outpatient clinics for almost 100% of the inhabitants of the country. The cohort includes 507 136 individuals with AF between 2008 and 2012 aged >18 years who survived the first 30 days following diagnosis. Of 507 136 subjects, there were 423 109 (83.4%) with non-valvular AF and 84 027 (16.6%) with valvular AF. The prevalence was 0.80% in non-valvular AF and 0.28% in valvular AF; in 2012 the incidence of non-valvular AF (0.17%) was higher than valvular AF (0.04%). All-cause mortality was 19.19% (97 368) and 11.47% (58 161) at 1-year after diagnosis of AF. There were 35 707 (7.04%) ischaemic stroke/TIA/thromboembolism at baseline and 34 871 (6.87%) during follow-up; 11 472 (2.26%) major haemorrhages at baseline and 10 183 (2.01%) during follow-up, and 44 116 (8.69%) hospitalizations during the follow-up.

Conclusion The TRAF cohort is the first population-based, whole-country cohort of AF epidemiology, quality of care and outcomes. It provides 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 of atrial fibrillation • CHA_2DS_2Vasc • Population-based cohort

Introduction

Atrial fibrillation (AF) is the most common sustained clinical 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 in the developed countries with an increase in the 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

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What's new?

- In this cohort, a whole country data of atrial fibrillation epidemiology is presented.
- This study reported the causes and impact of treatments on the incidence and outcomes of AF in a developing country.
- This cohort demonstrated that low incidence of AF, higher frequency in women and inappropriate/inadequate use of oral anticoagulants in a developing country.

among developing countries. Typically, these countries have younger populations and rapidly embrace new health technologies. In addition, most of the randomized data that are used to report the epidemiological features of AF, 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 utilization, 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 over the age of 18 in the country. The overall aim of the TuRkish Atrial Fibrillation (TRAF) cohort is to provide real life data about the prevalence, incidence, demographics, co-morbidities, treatments, quality of care and outcomes for all types of AF. Here in, 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, hospitalizations and mortality.

Methods

Data source

Data for the TRAF cohort were obtained from the Turkish claims and utilization 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 entered into the MEDULA database by physicians include patient demographics, prescription details, observed clinical events, outpatient clinics, inpatient hospitalizations and major clinical outcomes. For each hospitalization, the dates of admission and discharge, main diagnoses and major outcomes are recorded. The MEDULA 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 anonymized patient-level data.

Study population

We included all individuals with a diagnosis of AF who were aged over 18 years between 1 January 2008 and 31 December 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 presumably because their death would be unlikely to be associated with AF. 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 and Q232) or a history of valve surgery (Z95). 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 (I62.9), others) events were extracted. The ICD-10 codes used for the diagnostic categories can be seen in *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 utilization and outcomes data

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

Stroke risk schemes

We extracted patient-level information to enable the calculation of CHA_2DS_2Vasc stoke risk schemes for AF. Components of the CHA_2DS_2Vasc 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, vascular disease (prior acute myocardial infarction, peripheral arterial disease) and sex category.[3]

Using ICD-10 codes alone, heart failure, coronary artery disease, diabetes, hypertension and stroke can be ruled in but not necessarily ruled out. We used some review of additional data (e.g. physician notes or imaging studies) to confirm the diagnosis of valvular disease, arterial peripheral embolus, intracranial haemorrhage and deep venous thrombosis.[5]

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 χ^2-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 Spearman's correlation, where appropriate, was used to explore the associations between study parameters. Age- and sex-standardized rates of the incidence of AF were calculated. Generalized 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.

Table 1 ICD-10 codes and frequencies

Diagnosis	ICD-10 code	Frequency (%)
Heart failure	I50	226 545 (44.67)
Hypertension	I10-15	406 358 (80.13)
Diabetes mellitus	E10-14	103 305 (20.37)
Haemorrhagic stroke	I62.9	672 (0.13)
Ischemic stroke	I63	26 876 (5.30)
Stroke, unspecified	I64	5195 (1.02)
TIA	G45	15 943 (3.14)
Peripheral systemic embolism	I74	6765 (1.33)
Thromboembolic event	I63-64, G45, I74	35 707 (7.04)
Acute myocardial infarction	I21, I252	39 852 (7.86)
Ischemic heart disease	I20–25	347 241 (68.47)
Peripheral arterial disease	I70–73	35 524 (7.01)
Vascular disease	I21, I252, I65, I70-73	70 560 (13.91)
Valvular disease	I05-09, I33-39	84 027 (16.57)
Mitral stenosis	I342, I050, I052, Q232	17 647 (3.48)
Renal disease	N17-19 or local code for renal transplantation/dialysis	41 718 (8.23)
Chronic pulmonary disease	J40-70	152 278 (30.03)
Emphysema/COPD	J43-44	152 278 (30.03)
Hyperthyroidism	E05	34 726 (6.85)

Results

Between 2008 and 2012, the estimated prevalence of AF in the country was 1.08%. *Figure 1* shows Gender distribution segmented with the incidence years for all AF patients. Age distribution of AF is demonstrated in *Figure 2*.

Of 507 136 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 423 109 (83.4%) with non-valvular AF and 84 027 (16.6%) with valvular AF. *Of those with non-valvular AF*, 30 651 (7.24%) had lone AF. *Overall*, there were 2 360 191.75 person-years of follow-up over a mean of 55.85 (±0.0304) months. For *this cohort*, the mean age was 66.04 (±0.02) years, 57.14% were female. All-cause mortality was 19.19% (97 368) and 11.47% (58 161) all-cause mortality at 1-year after diagnosis of AF. There were 35 707 (7.04%) ischaemic stroke/TIA/thromboembolism at baseline and 34 871 (6.87%) during follow-up, 11 472 (2.26%) major haemorrhages at baseline and 10 183 (2.01%) during follow-up, and 44 116 (8.69%) hospitalizations during follow-up. The median (min-max) CHA_2DS_2Vasc score was 4 (0–9).

Non-valvular AF

For individuals with non-valvular AF, the mean age was 66.11 (±0.02) years, 55.92% were female. The prevalence was 0.80% and the incidence was 0.17% in 2012. The prevalence of non-valvular AF increased with increasing age. *Figure 3* shows the prevalence of non-valvular AF by age.

Among this group, the frequencies of baseline co-morbidities were hypertension 84.87%, heart failure 54.89%, COPD 31.94%, diabetes mellitus 19.74% and acute myocardial infarction 7.35% (*Figure 4*). One-year hospitalization rate following the diagnosis was 3.22% (13 612). A total of 27 909 (6.59%) patients had an ischemic stroke/TIA/thromboembolism after their diagnosis of non-valvular AF. The yearly rate of stroke/TE according to CHA_2DS_2Vasc score is shown in *Figure 5*. All-cause mortality at 1-year after diagnosis of non-valvular AF was 12.07% (51 068 individuals). Number and % of patients in each CHA_2DS_2Vasc score is given at *Table 2*.

Valvular AF

For subjects with valvular AF mean age was 65.68 (±0.045) years, 63.29% were female. The prevalence was 0.28%, the incidence was 0.04% in 2012. 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 6* shows the age distribution of valvular AF prevalence).

Major baseline co-morbidities for this group included hypertension (79.20%), heart failure (42.64%), COPD (29.64%), diabetes mellitus (20.49%), and acute myocardial infarction (7.96%) of the patients with valvular AF (*Figure 7*). One-year hospitalization rate after diagnosis of valvular AF was 5.58%. A total of 6962 patients (8.28%) had an ischemic stroke/TIA/thromboembolism after their diagnoses of valvular AF. All-cause mortality rate for the 5-years following the diagnosis of valvular AF was 17.7% (14 929 individuals).

Lone AF

Individuals without any comorbidity constituted the 7.24% (30 651) of the group with non-valvular AF. When we considered individuals with lone AF aged less than 60 years, the frequency was 4.93% (20 891).

However, all-cause mortality rate for the 5-year follow-up was 7.77% (2382) across all ages and 1.78% (372) 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 suggest that the prevalence and the incidence of non-valvular AF in Turkey is lower than that reported in Western 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%.[6–8] Our lower rate probably reflects the younger demographics of the Turkish population in concert, and a

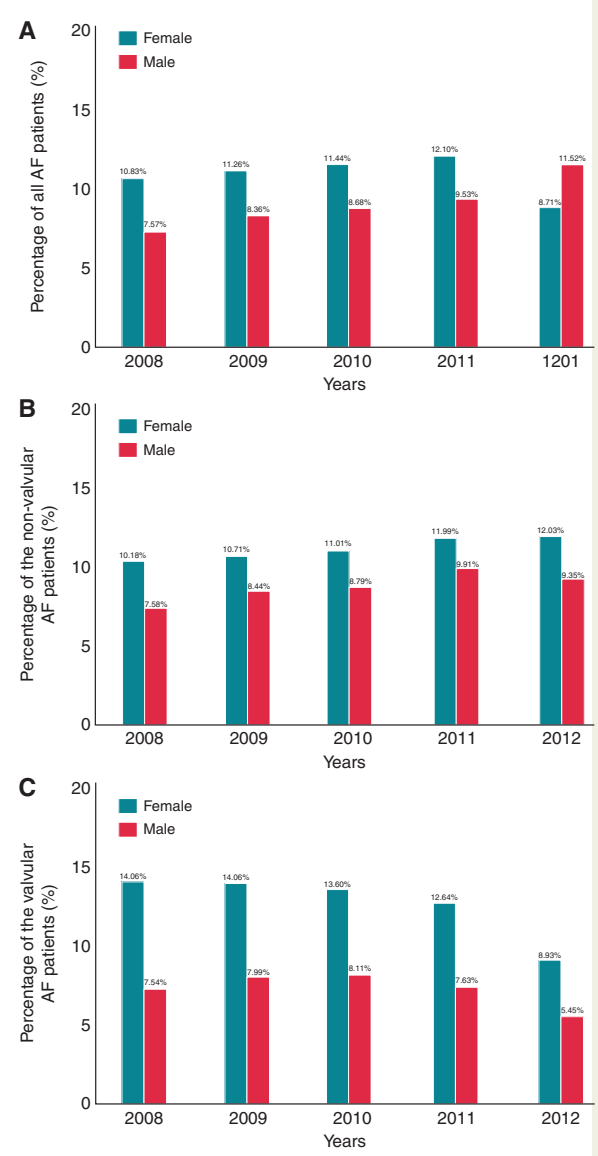

Figure 1 Gender distribution segmented with the incidence years for all AF patients ($N = 507\ 136$) (*A*), for non-valvular AF patients ($N = 423\ 109$) (*B*) and for valvular AF patients ($N = 84\ 027$) (*C*).

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.[9] This compares with a median age of 37.2 and 38.0 years and 13.3% and 16.7% over the ages of 65 years in Northern America and Europe, respectively.[10,11]

Although the prevalence of non-valvular AF was lower than that reported in the Western world, we found a higher prevalence of valvular AF in Turkey. Acute rheumatic fever and its complications, although significantly reduced, have not been eradicated yet. This is an important finding from our study which has critical public health repercussion should Turkey wish to address preventable valvular heart disease and associated valvular AF. Notwithstanding 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 the country. This burden will be driven by an aging and multi-morbid population in coming years.

In the previous reports from the Western healthcare systems, the prevalence of AF has been reported to be greater in men than women.[1] In the TRAF cohort, in contrast to the ATRIA study, Euro Heart Survey and Framingham study we found a higher frequency of non-valvular AF in women.[12–14] Although we do not have a clear explanation it might be related to the high prevalence of obesity, metabolic syndrome and cardiovascular diseases in Turkish women over the age of 40 as compared to the European Countries.[15]

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.[1,16] We found that the rate of death at 1 year was 7.04%.

The increasing incidence and prevalence of AF will continue to impose a considerable burden on the Turkish medical health-care system.[17–19] While we found a well-reported association among AF, increasing age and concomitant diseases such as hypertension, coronary artery disease, and heart failure,[20–22] data 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.[23] 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.[24] In another study, Wolf *et al.*[25] 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.*[26] 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.*[19] reported an adjusted relative risk for all-cause mortality among patients with an incident AF of 1.5–2, with higher relative risks in younger individuals and females.

The costs associated with AF patient care are high and are driven largely by the cost of hospitalization. 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.*,[27] more than half (51.9%) were hospitalized with non-fatal outcomes over a mean follow-up period of 24 months and 38.3% were hospitalized during the first year. Wu *et al.*[28–30] reported nearly half of the patients with AF required one inpatient visit over 1 year compared with 6.6% of a matched non-AF sample. In the study of Naccarelli *et al.*,[27] 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.

Potential limitations of this study should be addressed. The lower prevalence and incidence of AF in this study might be related to non-optimal screening for AF. This is a database study and some AF patients might be missed out.

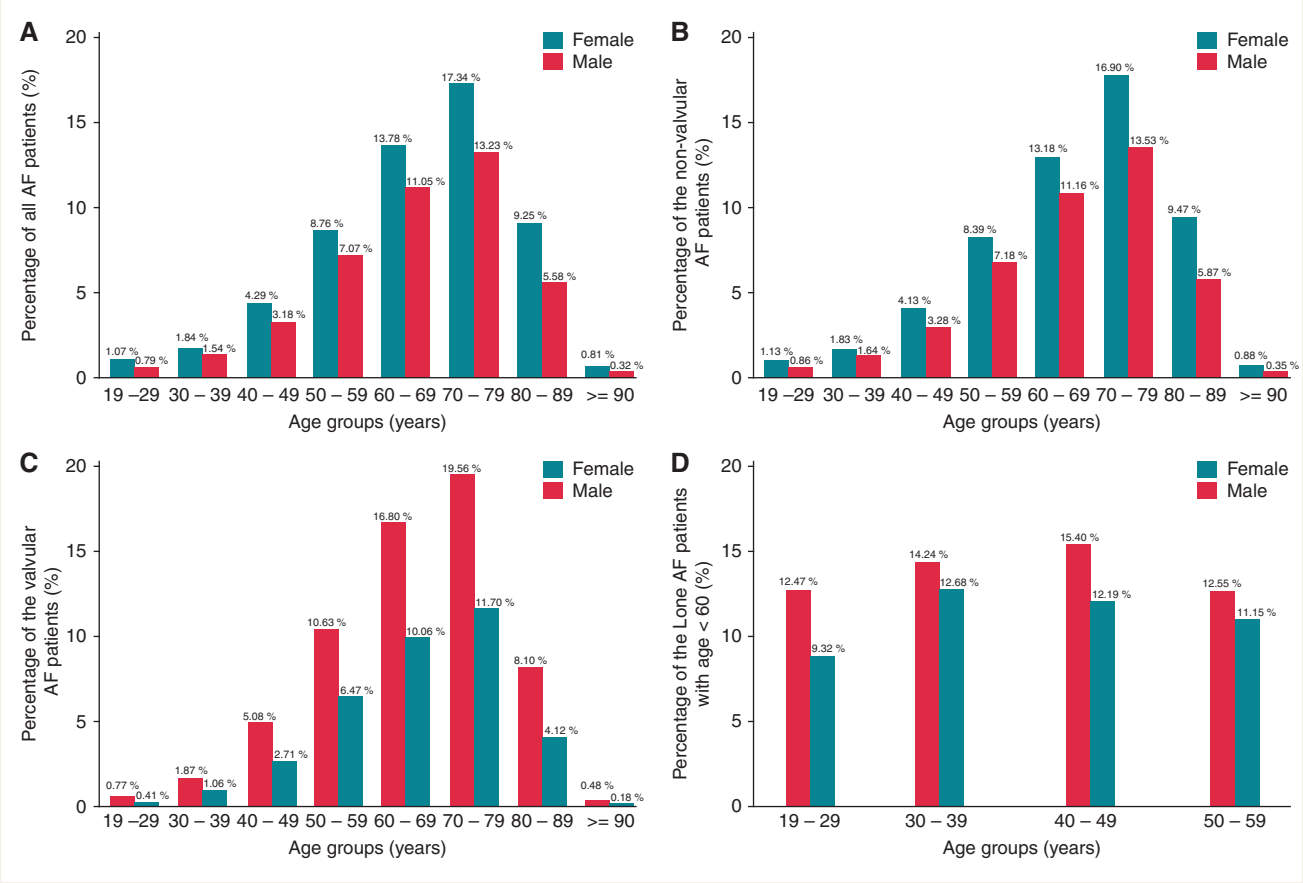

Figure 2 The distribution by age and gender in all AF patients (*A*), patients with non-valvular AF (*B*), patients with valvular AF (*C*) and patients with lone AF (*D*).

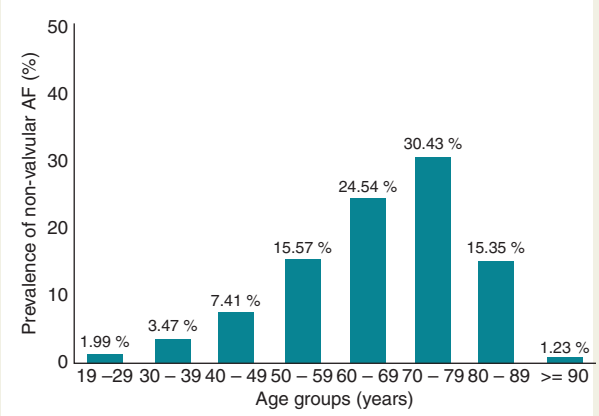

Figure 3 Prevalence of non-valvular AF by age.

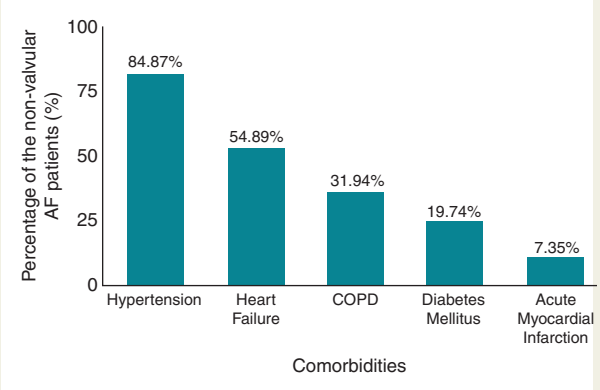

Figure 4 Baseline comorbidities in non-valvular AF patients.

Conclusion

The TRAF cohort provides real-life data in a whole country cohort of AF. It contains detailed information about incidence, prevalence, co-morbidities, treatments and outcomes. The difference in epidemiology in a developing country has been highlighted. The unique features included low incidence of AF, higher frequency in women. The increasing burden on the healthcare system with the ageing of the population is on the way.

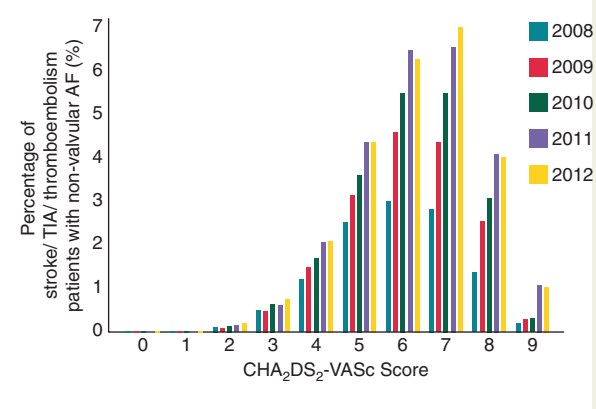

Figure 5 The distribution of risk score CHA_2DS_2Vasc for stroke/TIA/thromboembolism patients with non-valvular AF during 5-year follow-up.

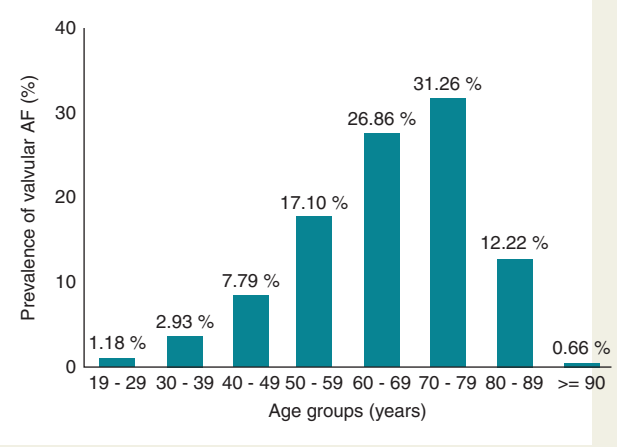

Figure 6 Age distribution of valvular AF prevalence.

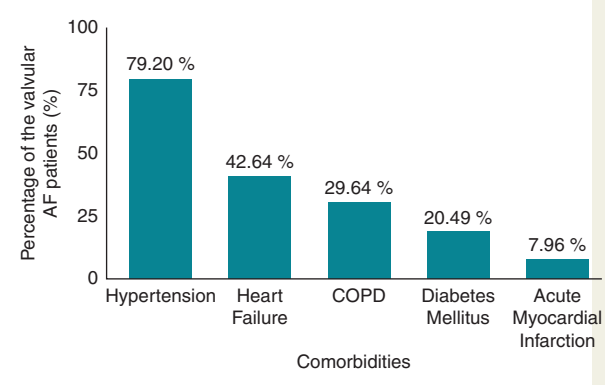

Figure 7 Comorbidities in valvular AF.

Conflict of interest: none declared.

References

1. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, *et al.* Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Europace* 2010;**12**:1360–420.
2. Ruigomez A, Johansson S, Wallander MA, Rodriguez LA. Incidence of chronic atrial fibrillation in general practice and its treatment pattern. *J Clin Epidemiol* 2002;**55**:358–63.
3. ICD 10 Codes. http://apps.who.int/classifications/icd10/browse/2010/en.
4. Drug ATC Index. http://www.whocc.no/atc_ddd_index/.
5. Birman-Deych E, Waterman AD, Yan Y, Nilasena DS, Radford MJ, Gage BF. Accuracy of ICD-9-CM codes for identifying cardiovascular and stroke risk factors. *Med Care* 2005;**43**:480–5.
6. Cowan C1, Healicon R, Robson I, Long WR, Barrett J, Fay M *et al.* The use of anticoagulants in the management of atrial fibrillation among general practices in England. *Heart* 2013;**99**:1166–72.
7. Lip GY, Laroche C, Popescu MI, Rasmussen LH, Vitali-Serdoz L, Dan GA *et al.* Improved outcomes with European society of cardiology guideline-adherent antithrombotic treatment in high-risk patients with atrial fibrillation: a report from the EORP-AF General Pilot Registry. *Europace* 2015;**17**:1777–86.
8. Kirchhof P, Breithardt G, Bax J, Benninger G, Blomstrom-Lundqvist C, Boriani G *et al.* A roadmap to improve the quality of atrial fibrillation management: proceedings from the fifth Atrial Fibrillation Network/European Heart Rhythm Association consensus conference. *Europace* 2016;**18**:37–50.
9. Tuik Data. http://www.tuik.gov.tr/UstMenu.do?metod=temelist.
10. Europa and North America population Data. http://www.census.gov/popest/data/national/asrh/2011/tables/NC-EST2011-01.xls.
11. Mandalenakis Z, Von Koch L, Eriksson H, Dellborg M, Caidahl K, Welin L *et al.* The risk of atrial fibrillation in the general male population: a lifetime follow-up of 50-year-old men. *Europace* 2015;**17**:1018–22.
12. Singer DE, Chang Y, Borowsky LH, Fang MC, Pomernacki NK, Udaltsova N *et al.* A new risk scheme to predict ischemic stroke and other thromboembolism in atrial fibrillation: the ATRIA study stroke risk score. *J Am Heart Assoc* 2013;**2**:e000250.
13. Lloyd-Jones DM, Wang TJ, Leip EP, Larson MG, Levy D, Vasan RS *et al.* Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. *Circulation* 2004;**110**:1042–6.
14. Nieuwlaat R, Capucci A, Camm AJ, Olsson SB, Andresen D, Davies DW *et al.* Atrial fibrillation management: a prospective survey in ESC member countries: the Euro Heart Survey on Atrial Fibrillation. *Eur Heart J* 2005;**26**:2422–34.
15. Obesity Data of Europa and Turkey. http://www.euro.who.int/en/healthtopics/noncommunicablediseases/obesity/data-and-statistics - http://beslenme. gov.tr/index.php?page=40.
16. Proietti M, Laroche C, Opolski G, Maggioni AP, Boriani G, Lip GY *et al.* 'Real-world' atrial fibrillation management in Europe: observations from the 2-year follow-up of the EURObservational research programme-atrial fibrillation general registry pilot phase. *Europace* 2016;**pii**:euw112.
17. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, *et al.* 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Europace* 2012;**14**:1385–413.
18. Heeringa J, van der Kuip DA, Hofman A, Kors JA, van Herpen G, Stricker BH *et al.* Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. *Eur Heart J* 2006;**27**:949–53.
19. Andersson T, Magnuson A, Bryngelsson IL, Frobert O, Henriksson KM, Edvardsson N *et al.* All-cause mortality in 272,186 patients hospitalized with incident atrial fibrillation 1995–2008: a Swedish nationwide long-term case-control study. *Eur Heart J* 2013;**34**:1061–7.
20. Wachtell K, Hornestam B, Lehto M, Slotwiner DJ, Gerdts E, Olsen MH *et al.* Cardiovascular morbidity and mortality in hypertensive patients with a history of atrial fibrillation: the Losartan Intervention For End Point Reduction in Hypertension (LIFE) study. *J Am Coll Cardiol* 2005;**45**:705–11.
21. Jabre P, Roger VL, Murad MH, Chamberlain AM, Prokop L, Adnet F *et al.* Mortality associated with atrial fibrillation in patients with myocardial infarction: a systematic review and meta-analysis. *Circulation* 2011;**123**:1587–93.
22. van den Berg MP, van Gelder IC, van Veldhuisen DJ. Impact of atrial fibrillation on mortality in patients with chronic heart failure. *Eur J Heart Fail* 2002;**4**:571–5.
23. Vidaillet H, Granada JF, Chyou P, Maassen K, Ortiz M, Pulido JN *et al.* A population-based study of mortality among patients with atrial fibrillation or flutter. *Am J Med* 2002;**113**:365–70.
24. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham heart study. *Circulation* 1998;**98**:946–52.

25. Wolf PA, Mitchell JB, Baker CS, Kannel WB, D'Agostino RB. Impact of atrial fibrillation on mortality, stroke, and medical costs. *Arch Intern Med* 1998;**158**:229–34.
26. Frost L, Engholm G, Moller H, Husted. Decrease in mortality in patients with a hospital diagnosis of atrial fibrillation in Denmark during the period 1980–1993. *Eur Heart J* 1999;**20**:1592–9.
27. Naccarelli GV, Johnston SS, Dalal M, Lin J, Patel PP. Rates and implications for hospitalization of patients >/=65 years of age with atrial fibrillation/flutter. *Am J Cardiol* 2012;**109**:543–9.
28. Wu EQ, Birnbaum HG, Mareva M, Tuttle E, Castor AR, Jackman W *et al.* Economic burden and co-morbidities of atrial fibrillation in a privately insured population. *Curr Med Res Opin* 2005;**21**:1693–9.
29. Wolowacz SE, Samuel M, Brennan VK, Jasso-Mosqueda JG, Van Gelder IC. The cost of illness of atrial fibrillation: a systematic review of the recent literature. *Europace* 2011;**13**:1375–85.
30. Reinhold T, Lindig C, Willich SN, Brüggenjürgen B. The costs of atrial fibrillation in patients with cardiovascular comorbidities – a longitudinal analysis of German health insurance data. *Europace* 2011;**13**:1275–80.