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Atrial Fibrillation In Middle-Eastern Arabs And South Asians: Studies From A 20-Year National Registry In Qatar

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Atrial Fibrillation In Middle-Eastern Arabs And South Asians: Studies From A 20-Year National Registry In Qatar

by

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Acknowledgment

I wish to dedicate this work to my father; God bless his soul, my ultimate teacher and supporter. He frequently told me ‘when there is a will, there is a way’.

I will not forget my family, wife and children, who endured long hours of my engagement with research and studies.

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Author's Declaration

At no time during the registration for the degree of *Doctor of Philosophy* has the author been registered for any other University award without prior agreement of the Doctoral College Quality Sub-Committee.

Work submitted for this research degree at the University of Plymouth has not formed part of any other degree either at the University of Plymouth or at another establishment.

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ABSTRACT

AMAR (MOHAMMAD AMIN) FARHAN SALAM

Atrial fibrillation in Middle-Eastern Arabs and South Asians: Studies from a 20-year National Registry in Qatar

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice accounting for approximately one-third of hospitalizations for cardiac rhythm disturbances and is associated with increased risk for stroke, heart failure and death. The epidemiology and clinical features of AF have primarily been characterized in whites of European-descent. The world literature on the epidemiology of AF among different ethnicities is very limited with most of the published reports of AF in non-white ethnicities focusing mainly on black (African-American) patients.

The current work represents structured and staged examination of AF in two ethnic groups where very limited literature is available on, namely: Middle Eastern Arabs and South Asians. My original contribution to knowledge includes identification of different aspects of AF in the targeted ethnic groups (Middle Eastern Arabs and South Asians), including: aetiologies; secular trends; cardiovascular risk factors; therapy; and outcome using data from a national registry of cardiovascular diseases in a Middle Eastern country over a 20-years period. In addition, the research undertaken focused on several other aspects peculiar to the effects of AF in these two ethnicities. This included; religious fasting, gender differences, and in high-risk patients including those with chronic kidney disease and acute myocardial infarction.

Results of the work fill literature gaps in the clinical features, management and outcomes of AF in the two targeted ethnicities, which serve as essential background for further research to improve outcomes. Moreover, the work included original contributions to general AF knowledge, namely in relation to the effects of fasting and lack of symptoms at presentations,

which enriches the world literature of AF. This thesis includes nine publications; seven original papers, one summary paper, and one literature review paper; all published in peer-reviewed journals.

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List of Original Publications

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II. **Salam AM**, AlBinali HA, Al-Mulla AW, Asaad N, Singh R, Al-Qahtani A, Al Suwaidi J. Women hospitalized with atrial fibrillation: gender differences, trends and outcome from a 20-year registry in a Middle Eastern country (1991-2010). Int J Cardiol. 2013 Sep 30;168(2):975-80. doi: 10.1016/j.ijcard.2012.10.041. Epub 2012 Nov 15. PMID: 23159409.

III. **Salam AM**, AlBinali HA, Al-Sulaiti EM, Al-Mulla AW, Singh R, Al Suwaidi J. Effect of age on treatment, trends and outcome of patients hospitalized with atrial fibrillation: insights from a 20-years registry in a Middle-Eastern country (1991-2010). Aging Clin Exp Res. 2012 Dec;24(6):682-90. doi: 10.3275/8757. Epub 2012 Nov 26. PMID: 23211770.

IV. **Salam AM**, Al BH, Singh R, Gehani A, Asaad N, Al-Qahtani A, Suwaidi JA. Atrial fibrillation in Middle Eastern Arab and South Asian patients hospitalized with acute myocardial infarction: experience from a 20-year registry in qatar (1991-2010). Acta Cardiol. 2013 Apr;68(2):173-80. doi: 10.1080/ac.68.2.2967275. PMID: 23705560.

V. **Salam AM**, Gersh BJ, AlBinali HA, Singh R, Asaad N, Al-Qahtani A, Suwaidi JA. The prognostic implications of lack of palpitations in patients hospitalised with atrial fibrillation: observations from a 20-year registry. Int J Clin Pract. 2014 Jan;68(1):122-9. doi: 10.1111/ijcp.12230. PMID: 24341306.

VI. **Salam AM**, AlBinali HA, Salim I, Singh R, Asaad N, Al-Qahtani A, Al Suwaidi J. Impact of religious fasting on the burden of atrial fibrillation: a population-based study. Int J Cardiol. 2013 Oct 3;168(3):3042-3. doi: 10.1016/j.ijcard.2013.04.131. Epub 2013 May 1. PMID: 23642825.

VII. Salim I, Al Suwaidi J, AlBinali HA, Singh R, Al-Qahtani A, Asaad N, **Salam AM**. Impact of Chronic Kidney Disease on the Presentation and Outcome of Patients Hospitalized With Atrial Fibrillation: Insights From Qatar. Angiology. 2018 Mar;69(3):212-219. doi: 10.1177/0003319717717849. Epub 2017 Jul 10. PMID: 28691505.

VIII. **Salam AM.** Atrial Fibrillation in Middle Eastern Arabs and South Asians: Summary of Published Articles in the Arabian Gulf. Heart Views. 2019 Oct-Dec;20(4):158-165. doi: 10.4103/HEARTVIEWS.HEARTVIEWS_116_19. Epub 2019 Nov 14. PMID: 31803372; PMCID: PMC6881872. [Publications` summary article].

IX. **Salam AM**, Kaddoura R, Salih V, Asopa S. Atrial fibrillation in Middle Eastern Arabs and South Asians: a scoping review. Rev Cardiovasc Med. 2021;22(4):1185-1196. doi:10.31083/j.rcm2204127 [Literature Review Paper].

1. INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice accounting for approximately one-third of hospitalizations for cardiac rhythm disturbances [1]. AF is associated with increased risk for stroke, heart failure and death. The global burden of AF is estimated at around 33.5 million with progressive increases in incidence, prevalence and AF-related mortality having major implications for healthcare costs and public health policy [2].

The epidemiology and clinical features of AF have primarily been characterized in whites of European-descent [3]. The world literature on the epidemiology of AF among different ethnicities is limited [4]. Moreover, most of the published reports of AF in non-white ethnicities have focused mainly on black (African-American) patients. Data about AF in Arabic and South-Asian populations is much more limited [5,6].

In my research I examined different aspects of AF, including: aetiologies; secular trends; cardiovascular risk factors; therapy; and outcome in two unique ethnicities that have not been adequately studied together previously (Middle Eastern Arabs and South Asians), using data from a national registry of cardiovascular diseases in a Middle Eastern country over a 20-years period. The research undertaken focused on several other aspects peculiar to the effects of AF in these two ethnicities. This included; religious fasting, gender differences, in patients with chronic kidney disease and acute myocardial infarction.

The current research was based on data from a national registry of cardiac disease in Qatar. Qatar is a small Arab country with a population of around 600,000 (2001 Census) and 1.6 million (2010 Census), consisting of Arabs (less than 40%) with the vast majority of non-Arabs being South Asians making it ideal for population-based studies in these two ethnicities. With the described database, all patients presenting with AF requiring hospitalization in the 20-year

period between 1991 and end of 2010 were retrospectively identified and data examined in these studies. Seven original studies are presented focusing on different aspects of AF in these two unique ethnicities; Middle Eastern Arabs and South Asians, using data from a national registry of cardiovascular diseases in Qatar over a 20-years period (1991-2010).

The first study looked at time trends of AF aetiologies, management and outcomes among the two ethnicities. There were significant variations in the prevalence of underlying cardiac aetiologies and associated risk factors. Overall, there was an increase in ischemic heart disease and a decrease in valvular heart disease in the latter years of the study but mortality trend was steady in both ethnic groups.

The second study focused on women with AF and examined gender differences, trends and outcomes. Women were older, had more diabetes mellitus and hypertension, while men had more ischemic heart disease. There was no gender preference in the use of anticoagulation. Gender was not an independent predictor of poor outcome.

The third study looked at the elderly patients aged above 70 years with AF compared to younger age groups. An alarming under-utilization of oral anticoagulants in the elderly group was observed despite the overwhelming evidence supporting their role in stroke prevention.

The fourth study examined the prognostic implications of lack of palpitations among patients hospitalized with AF. This study suggested, for the first time, -lack of palpitations- on presentation with AF, as a predictor of mortality independent of other risk factors or therapy.

The fifth study demonstrated that AF patients with chronic kidney disease (CKD) had different presentation symptoms and much higher morbidity and mortality, compared to those with normal renal function. CKD patients should therefore be screened for the presence of AF particularly when the reason for deterioration in not evident, even in the absence of palpitations.

The sixth study reported ethnic variations in AF complicating the course of acute myocardial infarction (AMI) in Middle-eastern Arabs and South Asians. AF occurred in 3.1% of Arabs with AMI and in 0.8% in South Asians. The study also demonstrated a significant impact of AF on survival in patients with AMI with increased in-hospital mortality and stroke rates. Advancing age was the major independent predictor of AF in AMI patients irrespective of ethnic origin.

The seventh study investigated the effects of religious fasting on the number of hospitalizations with AF taking hospitalizations as a reflection of AF incidence. It demonstrated for the first time that fasting has neutral effects on AF and suggested a favourable protective effect on ischemic AF.

Despite having the limitations inherent in all studies of historical, observational design, yet these studies shed light upon important aspects of AF presentations and outcomes in Middle Eastern Arab and South Asian ethnicities. In the process, several novel observations were reported and new questions were raised that warrant further investigations. Combined with a rigorous systematic scoping review of the literature on the subject as well as a published summary of the studies, the nine publications constitute therefore a ``significant original contribution`` in the field of AF research and cardiology in Arabs and Asians where very limited literature still exists.

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2. LITERATURE REVIEW

Most of the published literature on Atrial fibrillation (AF) originates from the northern hemisphere involving mainly Caucasian patients with limited studies in certain ethnicities and races. This scoping review was conducted to collect and summarize all pertinent evidence from the published scientific literature on AF in South Asians and Middle-Eastern Arabs. PubMed, Embase and Cochrane Library databases were included in our search. Out of 8995 records screened, 55 studies were finally selected; Middle East (n = 42) and South Asia (n = 13). Characteristics of the included studies were tabulated, and their data were summarized for study design, setting, enrolment period, sample size, demographics, prevalence or incidence of AF, co-morbidities, risk factors, AF types and symptoms, management, and outcomes. Identified literature gaps included paucity of community or population-based studies representative of these two ethnicities/races. In addition, studies that addressed ethnic/racial in-equality and access to treatment were lacking. Our study underscores the urgent need to study cardiovascular disorders, particularly AF, in South Asians and Middle-Eastern Arabs as well as in other less represented ethnicities and races.

2.1. Introduction

There has been an increasing interest in the effects of ethnicity and race on cardiovascular disorders. Patients from the same race and/or ethnicity share common genetic as well as environmental exposures. This may be responsible for the differences observed between different races/ethnicities in the incidence, presentation and outcomes of cardiovascular disorders as well as for the differences in response to therapy [1]. In addition, racial and ethnic inequalities and bias may also play an important role. Variations in access to care, economic status and education have all been linked to race/ethnicity and can affect awareness of disease and may lead in under-diagnosis and under-treatment.

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice accounting for approximately one-third of hospitalizations for cardiac rhythm disturbances [2]. Most of the published literature on AF originates from North America and Europe involving mainly Caucasian patients [3]. Other ethnicities are largely under-represented particularly South Asians and Middle-Eastern Arabs. Therefore, our aim was to perform a scoping review to identify and summarize current evidence on AF in these two ethnicities with the overarching objective to identify research gaps and inform future research in this area.

2.2. Methods

The objective of this scoping review was to assess the extent of the available literature of AF in South Asians and Arabs; identifying and summarizing clinical features and management. A preliminary search of MEDLINE and the Cochrane Database of Systematic Reviews was conducted and no current or underway systematic reviews or scoping reviews on the topic were identified.

A Scoping review is a systematic method of knowledge synthesis that examines and maps evidence on a specific subject matter, identifying key concepts, theories, sources of evidence, and research [4]. This scoping review follows the five steps proposed by Arskey and O'Malley [5]: 1)- identifying the research question, 2)- identifying relevant studies, 3)- selecting studies, 4)- collecting data, and 5)- mapping, summarizing and describing the results.

The reason we chose a scoping review over a systematic review for this study was the broader research question. While rigorous and detailed in-depth analysis of data is not normally required in scoping reviews, however, in our study a systematic inquiry was planned and conducted with synthesis of available evidence into several themes to comply with the study objectives.

2.2.1. Eligibility criteria

Studies that reported various aspects of AF including epidemiology, co-morbidities, risk factors, management and /or clinical outcomes in the Middle East or South Asia were included. Exclusion criteria included studies on sub-clinical AF, post-operative AF, genetics, cost-effectiveness, and smart devices. The countries in this review were categorized according to the world regions as per the World Health Organization (WHO) i.e., South-East Asia and Eastern Mediterranean regions [6]. For the purpose of this review, the terms Middle East(ern) and South Asia(n) will be used.

2.2.2. Search strategy

A comprehensive electronic literature search using MEDLINE, EMBASE, CENTRAL was performed on September 26, 2020. Boolean terms "OR" and "AND," Medical Subject Headings (MeSH), Emtree and broad keywords were used. The search terms combined and included "atrial fibrillation", "Middle East", "South Asia", "Arab", individual country and nationality. Search limitations were not applied. Reviews and meta-analyses, international registries and the references' lists of the retrieved articles were manually screened to identify additional relevant studies. The detailed search strategy is described in Table S1.

2.2.3. Study selection and data extraction

All records were reviewed on the titles and abstracts levels. Duplicate publications, posters, abstracts, irrelevant studies or those that did not meet the inclusion criteria were excluded. Relevant abstracts (n = 305) were screened and 84 of them were retrieved in full texts. After excluding 29 studies (table S2), the search strategy resulted in 55 studies [7-61] (Figures 1 and 2). However, 17 studies [45-61] were related to three registries [30,33,41] (Table S3) and were used when provided additional data or analysis. The included studies were tabulated, and their data were extracted for the study design, setting, enrolment period, sample size, demographics,

prevalence or incidence of AF, co-morbidities, risk factors, AF types and symptoms, management, and outcomes (Tables S3 – S7).

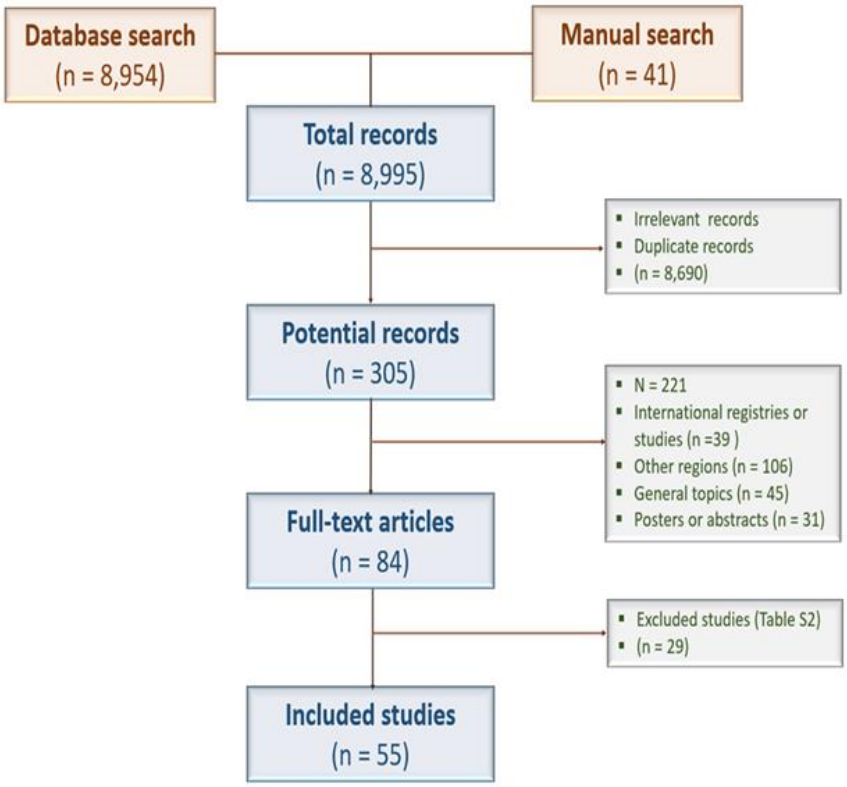

Figure 1 Study selection and exclusion

2.3. Results

The retrieve results are summarized in Fig 1. Of 8995 records screened, 55 studies were finally selected. The selected articles were categorized based on the region, i.e., Middle East (n = 42) and South Asia (n = 13). (Table S3) Studies from the Middle East included 15 single-centre [7-21] and four multi-centre [22-25] studies, five non-AF registries [26-30] with seven related publications [45-51], and three AF registries [31-33] with eight related publications [52-59]. Studies from South Asia included three single-centre [34-36] and two multi-centre [37,38]

studies, one non-AF [39] and five AF [40-44] registries. Two additional publications [60,61] came out from the COOL-AF registry [41]. By disregarding the 17 articles [45-61], the studies were performed in the following countries: India (n = 6), Kingdom of Saudi Arabia (KSA) (n = 7), Pakistan (n = 4), Thailand (n = 4), Iran (n = 4), Qatar (n=2), combined six adjacent Middle Eastern countries (n = 2), and one study for each of Bahrain, Egypt, Iraq, Jordan, Kuwait, Morocco, Nepal, Tunisia, and United Arab Emirates (UAE). The studies enrolled patients from the hospital settings, except in two studies [14,32], between 1989 and 2019. In the single- and multi-centre studies, sample size, age range and Female distribution of AF patients in the Middle Eastern and South Asian regions were 3514 and 9899 patients, 58.8 – 68.4 and 51.2 – 64.6 years, and 36.0 – 65.0% and 48.8 – 58.1%, respectively. The respective data from AF registries were 3181 and 9974 patients, 56.0 – 61.7 and 54.7 – 67.4 years, and 40.5 – 48.5% and 40.1 – 51.5%, respectively. Comparable age ranges and female proportions were seen in the studies (n = 7) and registries analyses (n = 5) that investigated AF in specified patient populations such as acute coronary syndrome [15,18,27], acute [26] and chronic heart failure [29], hypertension [38], and haemodialysis (HD) [22]. However, in two [20,36] out of four studies [12,20,28,36] that enrolled patients with stroke, patients were older (71 years), while patients with rheumatic heart disease (RHD) were younger (40.2 years) and with higher female proportion (72.3%) [39]. Characteristics of individual studies are presented in Table 1 and the overall characteristics are summarized in Table 2. Thematic summaries of data that included: co-morbidities and risk factors, AF types and symptoms at presentation, and management are summarized in tables 3-6, and details of data extracted in supplementary tables S3-S6.

2.3.1. Characteristics of Studies Included in Review

Table 1 General characteristics of studies on atrial fibrillation

First author	Enrolment period	Country	Study design	Sample size	Number of AF pts (%)	Age (year) Mean or median	Female (%)	Nationalities	Study Setting
Middle Eastern countries									
Single-centre studies (n = 15)									
Al-Turaiki et al, 2016 [7]	March 2014 to April 2014 (2 months)	Single-centre, KSA	Retrospective Cross-sectional	264	264 (100%)	68.4	54.5	Not specified	Hospital-based clinic
Anouassi et al, 2020 [8]	April 2015 to Feb 2019 (4 years)	Single- centre, UAE	Retrospective Cross-sectional	608	608 (100%)	65.2	41.4	Not specified	Hospital-based
Balaghi-Inalou et al, 2018 [9]	June 2016 to Jan 2017 (8 months)	Single-centre, Iran	Cross-sectional	120	120 (100%)	63.1	47.5	Iranian	Hospital-based
Ben Rejeb et al, 2019 [10]	Jan 2013 to Dec 2015 (3 years)	Single-centre, Tunisia	Observational Longitudinal	200	200 (100%)	58.8	65.0	Tunisian	Hospital-based Out-patient department
Bin Salih et al, 2011 [11]	Jan 2002 to Aug 2008 (6.6 years)	Single-centre, KSA	Retrospective Cross-sectional	720	720 (100%)	-	60.5	Not specified	Hospital-based (in- and out-patient)
Elkhatib et al, 2020 [12]	Jan 2017 to June 2018 (6 months)	Single-centre, Egypt	Case control	150	150 (100%)	62.4	49.3	Egyptian	Hospital-based Studied pts hospitalized with ischemic stroke
Garadah et al, 2011 [13]	Jan 2010 to Dec 2010 (1 year)	Single-centre (ER), Bahrain	Retrospective	7450	253 (3.4%)	**AF pts:** 59.4	**AF pts:** 36.0	ME: 59.3% SC: 40.7%[a]	Hospital-based Studied ethnicity groups in AF
Habibzadeh et al, 2004 [14]	April 2001 to Oct 2001	Single-centre, Iran	Prospective	463	13 (2.8%)	64.0	49.7	Iranian	community-based

First author	Enrolment period	Country	Study design	Sample size	Number of AF pts (%)	Age (year) Mean or median	Female (%)	Nationalities	Study Setting
	(6 months)					**AF pts:** 74.0	**AF pts:** 77.0		PHCC of an oil company
Khan et al, 2014 [15]	May 2013 to Oct 2013 (6 months)	Single-centre, Pakistan	Cross-sectional Descriptive	241	22 (9.1%)	- **AF pts:** 60.4	43.2 **AF pts:** 68.2	Pakistani	Hospital-based Studied pts hospitalized with AMI
Mashat et al, 2019 [16]	2010 to 2017 (7 years)	Single-centre, KSA	Retrospective	167	167 (100%)	63.3	56.9	Saudi: 41.3% Others: 58.7%	Hospital-based
Qanash et al, 2011 [17]	April 2010 to Oct 2010 (6 months)	Single-centre, KSA	Prospective Pilot	36	36 (100%)	-	-	Not specified	Hospital-based
Rehman et al, 2017 [18]	Oct 2015 to Sept 2016 (1 year)	Single-centre, Pakistan	Retrospective	536	49 (9.1%)	60.5 **AF pts:** -	44.4 **AF pts:** 59.1	Pakistani	Hospital-based Studied pts hospitalized with AMI
Ridha et al, 2005 [19]	Jan 2003 to May 2003 (5 months)	Single-centre, Kuwait	Retrospective	2830	120 (4.2%)	**AF pts:** 63.6	**AF pts:** 63.3%	Not specified	Hospital-based Studied features of AF types
Sadeghi et al, 2015 [20]	Between 2013 and 2014	Single-centre, Iran	Cross-sectional	900	100 (11.1%)	71.8	49.0%	Iranian	Hospital-based Studied pts hospitalized with ischemic stroke
Shatoor et al, 1998 [21]	Oct 1989 to Feb 1997 (7.5 years)	Single-centre, KSA	Retrospective	219	219 (100%)	Acute AF: 52.9 Chronic AF: 64.6	45.2	Not specified	Hospital-based
Multi-centre studies (n = 4)									
AlAwwa et al, 2020 [22]	Oct 2018 to Feb 2019 (5 months)	Multi-centre (n = 4), Jordan	Cross-sectional	231	18 (7.8%)	54.8 **AF pts**: 65.9	44.2 **AF pts**: 55.6	Jordanian: 86.6% Others: 13.4%	Hospital-based

First author	Enrolment period	Country	Study design	Sample size	Number of AF pts (%)	Age (year) Mean or median	Female (%)	Nationalities	Study Setting
									Studied undiagnosed AF in HD pts
Al-Radeef MY, 2019 [23]	July 2017 to Oct 2017 (4 months)	Multi-centre (n = 5), Iraq	Cross-sectional	100	100 (100%)	62.5	52.0	Iraqi	Hospital-based
Haq et al, 2009 [24]	April 2003 to June 2003 (8 weeks)	Multi-centre (n = 2), Pakistan	Prospective	3766	221 (5.8%)	**AF pts**: F: 66 M: 54	**AF pts**: 51.6	Afghani: 22.0% Indian: 3.0% Caucasian: 1.0% Rest: unknown	Hospital-based Acute admission
Ullah et al, 2015 [25]	Dec 2014 to Feb 2015 (3 months)	Multi-centre (n = 2), Pakistan	Cross-sectional Descriptive	205	205 (100%)	60.7	44.4	Pakistani	Hospital-based Studied anticoagulation practice
Non-AF registries (n = 5)									
Ajlan et al, 2018 [26]	Oct 2009 to Dec 2010 (15 months)	Multi-centre (n =18), KSA	HF registry (HEARTS)	2593	449 (17.8%)	61.4 **AF pts**: 65.2	34.4 **AF pts**: 46.3	Not specified	Hospital-based Studies AF in pts admitted with HF
Hersi et al, 2012 [27]	Oct 2008 to June 2009 (9 months)	Multi-centre (n = 65), 6 countries*	ACS registry (Gulf RACE-2)	7930	217 (2.7%)	56.8 **AF pts**: 64.6	21.3 **AF pts**: 34.1	Not specified	Hospital-based Studied AF in ACS pts
Imam et al, 2020 [28]	Jan 2014 to Oct 2017 (3.8 years)	Single-centre, Qatar	Stroke database	4079	260 (6.4%)	**AF pts**: 65.4	**AF pts**: 33.8	**AF pts**:$^{\Delta}$ Q: 11.6% ME/NA: 11.9% SA:3.0% Others: 4.7%	Hospital-based Studied AF in stroke pts

First author	Enrolment period	Country	Study design	Sample size	Number of AF pts (%)	**Age** (year) Mean or median	**Female** (%)	Nationalities	Study Setting
Ragbaoui et al, 2017 [29]	June 2006 to March 2015 (9 years)	Single-centre, Morocco	HF registry	3048	323 (10.6%)	**AF pts**: 52.0	**AF pts**: 32.6	Moroccan	Hospital-based Studied AF in pts with chronic HF
Cardiology and Cardiovascular Surgery Database[#]									
Dabdoob et al, 2007[§] [45]	Jan 1991 to 2002 (10 years)	Single-centre, Qatar	Registry (CCU)[#]	971	971 (100%)	55.6	F > M	Qatari	Hospital-based Reported data for Qatari pts
Salam et al, 2012 [30]	Jan 1991 to Dec 2010 (20 years)	Single-centre, Qatar	Registry	41453	3848 (9.3%)	Reported by age groups	By age groups	Reported by age groups	Hospital-based Studied effect of age
Salam et al, 2013 [46]	Jan 1991 to Dec 2010 (20 years)	Single-centre, Qatar	Registry	41438	3849 (9.3%)	**AF pts**: **F:** 59 **M:** 54.5	**AF pts**: 36.8%	**F**: ME: 86.1% SA: 6.1% Others: 7.8% **M**: ME: 67.1% SA: 19.0% Others: 13.7%	Hospital-based Studied gender disparity
Salam et al, 2013 [47]	Jan 1991 to Dec 2010 (20 years)	Single-centre, Qatar	Registry	41438	3405 (8.2%)[&]	**AF pts**: ME: 58 SA: 49	-	ME: 83.9% SA: 16.1%	Hospital-based Studied ethnicity groups in AF
Salam et al, 2013 [48]	Jan 1991 to Dec 2010 (20 years)	Single-centre, Qatar	Registry	12881 **AMI**	227 (1.8%) **AF** during hospitalization	**AF pts**: ME: 69 SA: 54 Others: 59	**AF pts**: 30.4	**AF pts**: ME: 68.7% SA: 21.1% Others: 10.1%	Hospital-based Studied ethnicity groups in AF pts hospitalized with AMI
Salam et al, 2013 [49]	Jan 1991 to Dec 2010 (20 years)	Single-centre, Qatar	Registry	1718	1718 (100%)	61	48.9	Qatari	Hospital-based Studied Qatari pts hospitalized with AF in the

First author	Enrolment period	Country	Study design	Sample size	Number of AF pts (%)	**Age** (year) Mean or median	**Female** (%)	Nationalities	Study Setting
									holy month of Ramadan
Salam et al, 2014 [50]	Jan 1991 to Dec 2010 (20 years)	Single-centre, Qatar	Registry	41438	3850 (9.3%) Palpit'n: 44.8% None: 55.2%	**AF pts**: Palpit'n: 51 None: 61	**AF pts**: 36.8	Not specified	Hospital-based Studied lack of palpitation at presentation
Salim et al, 2018 [51]	Jan 1991 to Dec 2012 (22 years)	Single-centre, Qatar	Registry	5201 **AF**	264 (5.1%) **CKD+AF**	CKD: 67 No CKD: 56	-	Not specified	Hospital-based Studied AF pts with CKD
AF registries (n = 3)									
Heidarali et al, 2020 [31]	Feb 2017 to Feb 2018 (1 year)	Nationwide cohort, Iran	Registry (IRAF)	738	738 (100%)	Fam: 51.0 Non-fam: 61.0	Fam: 44.0 Non-fam: 37.0	Iranian	Hospital-based Studied familial AF (15.3%)
Hersi et al, 2015 [32]	April 2011 to Nov 2011 (8 months)	Multi-centre (n = 18), KSA	Registry (SAS)	400	400 (100%)	61.7	48.5	Saudi: 84.2%	Community- and hospital-based
Gulf SAFE registry[$]									
Apostolakis et al, 2013[§] [52]	Oct 2009 to June 2010 (8 months)	Multi-centre (n = 23; ER), 6 countries[$]	Registry	2043	1721 (84%) **NVAF**	-	-	Not specified	Hospital-based Studied stroke risk
Domek et al, 2020 [53]	Oct 2009 to June 2010 (8 months)	Multi-centre (n = 23; ER), 6 countries	Registry	2043	2043 (100%)	57.0	48.0	Not specified	Hospital-based Studied impact of DM history (30%)
Domek et al, 2020 [54]	Oct 2009 to June 2010 (8 months)	Multi-centre (n = 23; ER), 6 countries	Registry	2043	603 (30%) **DM**	63.4	52.2	Not specified	Hospital-based Studied compliance to

First author	Enrolment period	Country	Study design	Sample size	Number of AF pts (%)	Age (year) Mean or median	Female (%)	Nationalities	Study Setting
									ABC pathway (DM pts)
Gumprecht et al, 2020 [55]	Oct 2009 to June 2010 (8 months)	Multi-centre (n = 23; ER), 6 countries	Registry	2021	2021 (100%)	56.7	47.9	Not specified	Hospital-based Studied compliance to ABC pathway
Li et al, 2019 [56]	Oct 2009 to June 2010 (8 months)	Multi-centre (n = 23; ER), 6 countries	Registry	2043	1740 (85%) **NVAF**	57.7	46.3	Not specified	Hospital-based Compared findings with Darlington AF registry (UK)
Miyazawa et al, 2019 [57]	Oct 2009 to June 2010 (8 months)	Multi-centre (n = 23; ER), 6 countries	Registry	2043	1860 (91%) **NVAF**	56.4	48.0	Not specified	Hospital-based Studied impact of stroke history (15.4%)
Shehab et al, 2017 [58]	Oct 2009 to June 2010 (8 months)	Multi-centre (n = 23; ER), 6 countries	Registry	2043	2043 (100%)	F: 58.5 M: 55.1	48.0	Not specified	Hospital-based Studied gender disparity
Zubaid et al, 2011 [33]	Oct 2009 to June 2010 (8 months)	Multi-centre (n = 23; ER), 6 countries	Registry	2043	2043 (100%)	57.0	48.0	Not specified	Hospital-based Registry's baseline characteristics
Zubaid et al, 2015 [59]	Oct 2009 to June 2010 (8 months)	Multi-centre (n = 23; ER), 6 countries	Registry	2043	1721 (84%) **NVAF**	59.0	44.4	Not specified	Hospital-based Studied one-year outcomes of NVAF pts
South Asian countries									
Single-centre studies (n = 3)									

First author	Enrolment period	Country	Study design	Sample size	Number of AF pts (%)	Age (year) Mean or median	Female (%)	Nationalities	Study Setting
Bhardwaj et al, 2012 [34]	April 2006 to March 2008 (2 years)	single-centre, India	Prospective	137	137 (100%)	51.2	55.4	Indian	Hospital in- and out-patients ECHO study to determine the cause of AF
Dhungel et al, 2017 [35]	Aug 2013 to July 2016 (3 years)	Single-centre, Nepal	Cross-sectional Descriptive	205	205 (100%)	63.9 **NVAF**: 69.6 **Valvular**: 46.7	48.8 **NVAF**: 45.2 **Valvular**: 68.6	Nepalese	Hospital-based Studied NVAF vs valvular AF
Srisilpa et al, 2020 [36]	Between 2012 and 2017 (5 years)	Single-centre, Thailand	Retrospective Cohort	119	119 (100%)	71	60.9	Thai	Hospital-based Studied pts with AF-associated stroke
Multi-centre studies (n = 2)									
Apiyasawat et al, 2015 [37]	Han 2005 to Dec 2005 (1 year)	Multi-centre, Thailand	Retrospective	8981	8981 (100%)	64.6	58.1	Thai	Hospital-based Pts hospitalized for AF
Krittayaphong et al, 2016 [38]	Between 2011 and 2012	Multi-centre (n = 831), Thailand	Cross-sectional	13207 (pts with ECG)	457 (3.4%)	**AF pts**: 63.6	**AF pts**: 64.3	Thai	Hospital in- and out-patients Studied AF in hypertensive pts
Non-AF registries (n = 1)									
Negi et al, 2018 [39]	Since 2011; ongoing (6 years)	Single-centre, India	Registry (HP-RF/RHD)	1918	459 (23.9%)	40.2	72.3	Indian	Hospital-based Studied AF in RF/RHD pts
AF registries (n = 5)									
Charantharayil et al, 2019 [40]	April 2016 to April 2017	Multi-centre (n = 53), India	Registry (Kerala AF)	3421	3421 (100%)	65.0	51.0	Indian	Hospital-based

First author	Enrolment period	Country	Study design	Sample size	Number of AF pts (%)	Age (year) Mean or median	Female (%)	Nationalities	Study Setting
	(1 year)								
Krittayaphong et al, 2018 [41]	2014 to 2017 (3 years)	Multi-centre (n = 24), Thailand	Nationwide registry (COOL-AF)	3218 **NVAF**	3218 (100%)	67.3	41.8	Thai	Hospital-based
Krittayaphong et al, 2020 [60]	2014 to 2017 (3 years)	Multi-centre (n = 27), Thailand	Nationwide registry (COOL-AF)	3327 **NVAF**	3327 (100%)	67.4	41.9	Thai	Hospital-based Studied adherence to OAC
Krittayaphong et al, 2019 [61]	2014 to 2017 (3 years)	Multi-centre (n = 24), Thailand	Nationwide registry (COOL-AF)	3218 **NVAF**	3218 (100%)	Older: 74.6 Younger: 56.0	Old: 46.3 Young: 34.7	Thai	Hospital-based Studied OAC in elderly
Narasimhan et al, 2016 [42]	Feb 2010 to March 2010 (2 months)	Multi-centre (n = 15), India	From a global registry of 26 countries (RealiseAF)	301	301 (100%)	59.9	47.5	Indian	Hospital out-patients (64.5%) and in-patients (35.5%)
Sawhney et al, 2018 [43]	Aug 2012 to Aug 2016 (4 years)	Multi-centre (n = 26), India	From a global registry of 35 countries (GARFIELD-AF)	1388 **NVAF**	1388 (100%)	65.8	40.1	Indian	Hospital-based (98.0%) and office-based practice (8.0%)
Vora et al, 2017 [44]	July 2011 to Aug 2012 (14 months)	Multi-centre (n = 24), India	National registry (IHRS-AF)	1537	1537 (100%)	54.7	51.5	Indian	Hospital-based

* Six countries: Bahrain, Saudi Arabia, Qatar, Oman, United Arab Emirates, and Yemen

Δ Nationalities in all stroke cohort: Qatari: 16.5%, ME/NA: 19.4%, SA: 51.6%, Others: 12.5%

The registry name has been changed from Coronary Care Unit to Cardiology and Cardiovascular Surgery Database. Since it is non-AF, no baseline characteristics in AF patients were published.

& The patients' number that was eligible for the study from 3849 patients (9.3%)

$ Six countries: Bahrain, Kuwait, Qatar, Oman, United Arab Emirates, and Yemen (an ER-based registry)

§ Published as letter to editor

ABC; Atrial fibrillation Better Care, ACS; acute coronary syndrome, AF; atrial fibrillation, AFVHD; atrial fibrillation of valvular heart disease, AMI; acute myocardial infarction, CCU; Coronary Care Unit, CKD; chronic kidney disease, DM; diabetes mellitus, ECG; electrocardiogram, ECHO; echocardiography, ER; emergency room, ESRD; end-stage renal disease, F; female, Gulf RACE-2; second Gulf Registry of Acute Coronary Events, Gulf SAFE; Gulf Survey of Atrial Fibrillation Events, HEARTS; Hearts Function Assessment Registry Trial in Saudi Arabia, HD; haemodialysis, HF; heart failure, HP-RF/RHD; The Himachal Pradesh- Rheumatic Fever/Rheumatic Heart Disease Registry, ICU; intensive care unit, IHRS-AF; Indian Heart Rhythm Society-Atrial Fibrillation, IRAF; Iranian registry of atrial fibrillation, KSA; Kingdom of Saudi Arabia, M; male, ME; Middle Eastern, ME/NA; Middle Eastern/North African, NVAF; non-valvular atrial fibrillation, OAC; oral anticoagulant, palpit'n; palpitation, PHCC; Primary health care centre, pts; patients, RealiseAF; Real Life global Survey Evaluating patients with atrial fibrillation, RF; rheumatic fever, RHD; rheumatic heart disease, SA; South Asian, SAS; Saudi Atrial Fibrillation Survey, UAE; United Arab Emirates, UK; United Kingdom.

Table 2 Characteristics of studies on AF summary

	Single- and multi-centre studies*		**Non- AF registries**		**AF registries**	
	ME region	SA region	ME region	SA region [39]	ME region	SA region
Number of studies	17	5	5	1	3	5
Enrolment period	1989 – 2019	2005 – 2017	1991 – 2017	Ongoing since 2011	2009 – 2018	2010 – 2017
Enrolment duration	8 week – 7.5 year	1 – 5 years	9 months – 22 years	-	8 month – 1 year	2 month – 4 years
Sample size	36 – 7450	119 – 13207	2593 – 41453	1918	400 – 2043	301 – 3421
Number of AF patients	3514	9899	5097	459	3181	9974
Incidence/Prevalence	2.8 – 5.8%	3.4%**	2.7 – 17.8%	23.9%	-	-
Age (year)	58.8 – 68.4	51.2 – 64.6	52.0 – 67.0	40.2	56.0 – 61.7	54.7 – 67.4
Female sex (%)	36.0 – 65.0%	48.8 – 58.1	30.4 – 48.9%	72.3%	40.5 – 48.5	40.1 – 51.5%

* Data from studies that investigated AF in specified patient populations (e.g., stroke) are not included in this table unless stated. [12,15,20,22,36,38]

** In hypertensive patients [38]

Abbreviations: AF; atrial fibrillation, ME; Middle Eastern, SA; South Asian

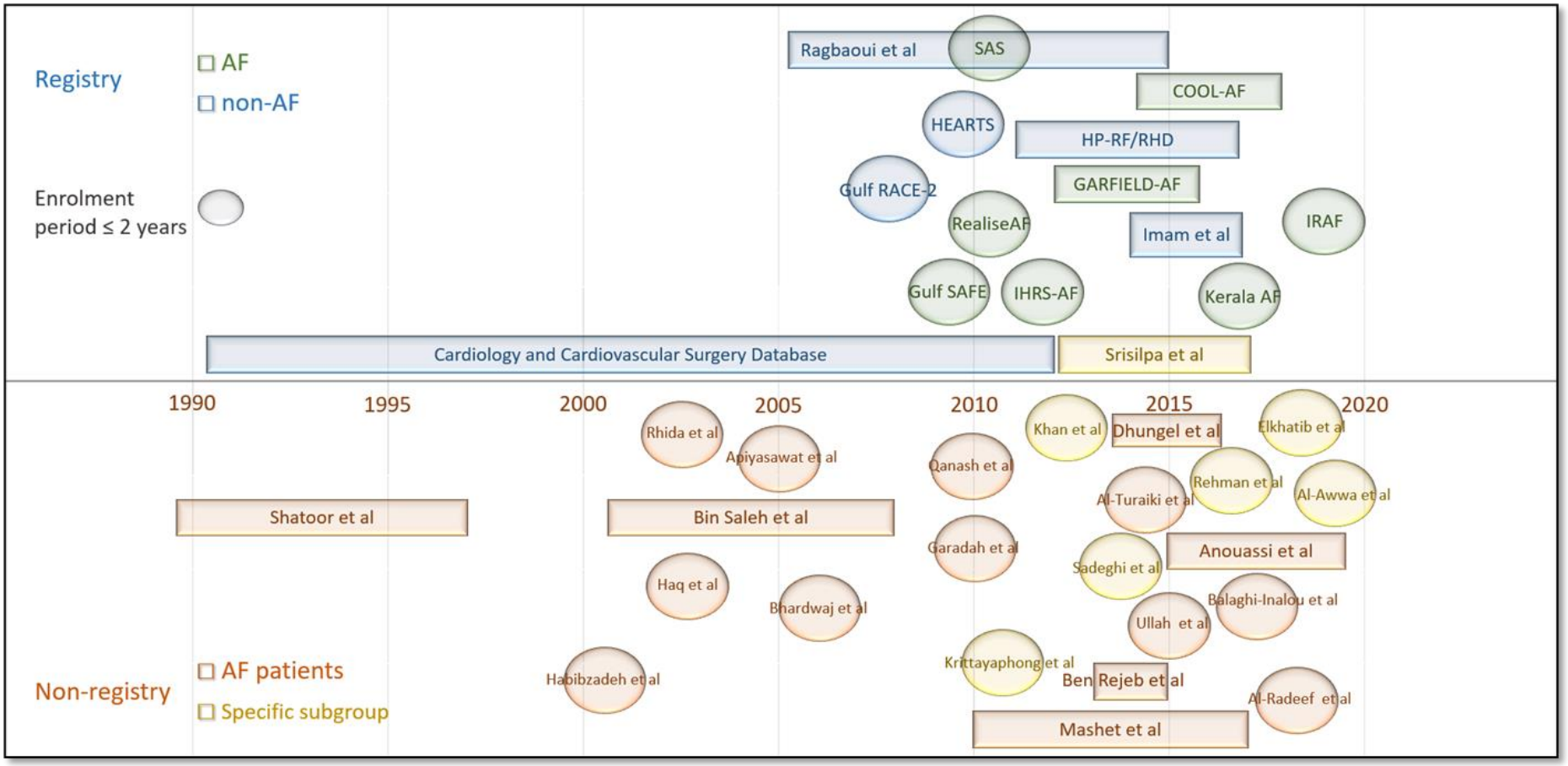

Figure 2 The selected studies. Visual summary of the studies: AF or non-AF registry (Top) and single- or multi-centre non-registry (Bottom) studies. The studies enrolled either AF patients only or specified subgroups which included proportion of patients with AF. The studies which are represented in an oval shape have an enrolment period of two years or less. Abbreviations/acronyms: AF, atrial fibrillation; COOL-AF Cohort of Antithrombotic Use and Optimal INR Level in Patients With Non-Valvular Atrial Fibrillation in Thailand; GARFIELD-AF, Global Anticoagulant Registry in the FIELD-Atrial Fibrillation; Gulf RACE-2, second Gulf Registry of Acute Coronary Events; Gulf SAFE, Gulf Survey of Atrial Fibrillation Events; HEARTS, Hearts Function Assessment Registry Trial in Saudi Arabia, HP-RF/RHD, Himachal Pradesh- Rheumatic Fever/Rheumatic Heart Disease; IHRS-AF, Indian Heart Rhythm Society-Atrial Fibrillation; IRAF, Iranian registry of atrial fibrillation; RealiseAF, Real Life global Survey Evaluating patients with atrial fibrillation; SAS, Saudi Atrial Fibrillation Survey.

2.3.2. Incidence and prevalence of AF

Overall, the incidence and prevalence of AF was reported in association with other diseases. The overall incidence of AF during hospitalization was 1.8% in patients admitted with acute myocardial infarction (AMI) in Qatar [48], with the incidence in Arabs being higher than that in South Asians (3.1% vs. 0.8%). From the earlier data of the same Qatari registry (1991 to 2002) [45], the overall annual incidence among Qataris was higher than that of other nationalities (12% vs. 8.0%). However, the rate (8.0 – 9.3%) remained consistent over years for the overall patient population i.e., hospitalized with acute cardiac illness [30,46,47,50]. The incidence of AF in the Gulf RACE-2 was 2.7% among patients hospitalized with acute coronary syndrome (ACS) [27]. While two studies from Pakistan [15,18] reported similar frequency of 9.1% each in patients hospitalized with AMI. The prevalence of AF among general hospital admissions was 3.4% in Bahrain [13], 4.2% in Kuwait [19], and 5.8% in Pakistan [24]. Whereas, a lower prevalence of 2.8% was reported in the only study that was conducted in a primary health care centre in Iran [14]. The prevalence of AF was 7.8% among patients on maintenance haemodialysis in Jordan [22], and 10.6% in patients with chronic heart failure in Morocco [29]. In Iran, the prevalence of AF among patients with stroke was 11.1% [20], while in Qatar, it was 6.4%, 2.6% of stroke patients were newly diagnosed with AF [28]. The highest AF prevalence reported were 17.8% in patients hospitalized with heart failure [26], and 23.9% in patients with RHD [39].

2.3.3. Characteristics of AF patients

2.3.3.1. Co-morbidities and risk factors

The most common co-morbidities associated with AF were hypertension, diabetes mellitus, heart failure and stroke which were comparable between the Middle Eastern and the South Asian registries (hypertension 52.0 – 63.0% and 31.4 – 68.5%, diabetes mellitus 30.0 – 48.0

and 16.1% - 36.2%, heart failure 27.0 – 31.7% and 15.5 – 27.2%, stroke 9.0 – 13.0% and 9.1 – 17.8%. Analyses from the Gulf SAFE registry [33] showed similar frequencies of the first three aforementioned co-morbidities in patients with stroke [57], and similar frequencies of hypertension and heart failure in patients with diabetes mellitus [54]. In non-AF registries, AF patients with stroke [28] and acute heart failure [26] had higher frequencies of both hypertension (72.3%) and diabetes (67.7%, included pre-diabetics), respectively, but not AF patients with chronic heart failure [29] or ACS [27]. Valvular heart diseases were more prominent in South Asia (40.7 – 50.3% versus 8.0 – 24.0%) than in Middle East. In the non-registry studies, there were noticeable variations in the reported frequencies of co-morbidities accompanied with variations in the terms of definitions used for the associated conditions. The mean HAS-BLED score ranged between 1.1 and 1.9 across the studies, while mean stroke risk scores CH2ADS2-VASc between 2.3 and 4.1, and CHADS2 between 1.6 and 2.3, with majority of patient had high stroke risk i.e., CHADS2 ≥ 2 in 36.7 to 71.0% of patients.

Table 3 Co-morbidities and risk factors in AF patients

Morbidity/Risk	**Single- and multi-centre studies ***		**AF registries**	
	ME region	SA region	ME region	SA region
Heart failure	14.0 – 45.6%	12.3 – 56.5%	27.0 – 31.7%	15.5 – 27.2%
Hypertension	23.7 – 79.5%	10.2 – 30.5%	52.0 – 63.0%	31.4 – 68.5%
Diabetes mellitus	12.0 – 68.3%	5.0 – 15.0%	30.0 – 48.0%	16.1 – 36.2%
Prior stroke	11.7 – 23.0%	0.6% [37]	9.0 – 13.0%	9.1 – 17.8%
CAD/IHD	3.5 – 55.8%	13.6% [35]	28.0 – 28.5%	5.4 – 34.8%
Valvular heart disease	23.6 – 58.7%	5.1 – 14.9% [34,35]	8.0 – 24.0%	40.7 – 50.3% [42,44]
Chronic kidney disease	18.9 – 36.8%	1.3 – 1.8% [35,37]	-	4.5 – 10.3%
Smoking	22.7 – 42.0%	-	23.0% [55]	16.0 – 18.6% [42, 43]
HAS-BLED score (mean)	1.2 – 1.9	-	1.1 [33]	1.5 – 1.6
CH_2ADS_2-VASc score (mean)	2.6 – 4.1	1.8 [37]	2.3 [33]	2.9 – 3.0

$CHADS_2$ score (mean)	2.0 – 2.3	-	1.6 [33]	1.8 [41]
$CHADS_2$ score = 0	5.0%	-	28.5% [33]	11.6 – 27.2%
$CHADS_2$ score = 1	24.0 – 26.0%	-	27.5% [33]	19.9 – 36.2%
$CHADS_2$ score ≥ 2	69.0 – 71.0%	-	44.0% [33]	36.7 – 68.5%

* Data from studies that investigated AF in specified patient populations (e.g., stroke) are not included in this table unless stated. [12,15,20,22,36,38]

Abbreviations: AF; atrial fibrillation, CAD; coronary heart disease, IHD; ischemic heart disease, ME; Middle Eastern, SA; South Asian

2.3.3.2. Types and symptoms of AF

There were few studies that reported the types and symptoms of AF. The frequency of new onset AF was reported in two Middle Eastern studies as 27.0% [24] and 59.0% [13], which was higher than that reported in AF registries [32,33,41,42,44]. The proportion of patients with permanent AF was higher in AF registry studies as compared to non-registry studies. The proportion of patients with persistent AF was higher in the latter studies. The most common symptoms at presentation were palpitation and dyspnea in more than half of the patients across the studies (Tables 3 and S5). A single-centre study from Nepal [35] reported AF types and symptoms in patients with valvular (24.9%) and non-valvular AF (75.1%). Paroxysmal AF was more common in non-valvular AF (55.2% versus 7.8%), while permanent AF was more common in valvular AF (51.0% versus 10.4%). Symptoms did not differ between the two groups.

Table 4 AF types and symptoms at presentation

AF type/symptom	**Single- and multi-centre studies***		**AF registries**	
Type	**ME region**	**SA region**	**ME region**	**SA region**
New onset	27.0 – 59.0% [13,24]	-	13.0 – 37.0%	2.3 – 14.3%
Paroxysmal	27.0 – 48.0%	-	17.0 – 24.5%	16.4 – 39.4%
Persistent	26.0 – 58.4%	41.6% [34]	10.0 – 17.5%	10.4 – 33.0%
Permanent	28.0 – 32.0%	58.4% [34]	33.0 – 45.0%	8.5 – 47.2%
Symptoms				
Palpitation	24.5 – 48.0% **	-	21.3% [32]	55.0% [42]
Dyspnea	14.0 – 59.3% **	-	20.5% [32]	66.0% [42]
Chest pain	12.0 – 38.0% **	-	-	21.0% [42]
Dizziness/syncope	6.0 – 18.0% **	-	20.5% [32]	23.1% [42]
Fatigue	5.0%&	-	13.3% [32]	48.7% [42]

* Data from studies that investigated AF in specified patient populations (e.g., stroke) are not included in this table unless stated. [12,15,20,22,36,38]
** Ref D was excluded as the percentages reported were skewed from the general trend across the studies
Abbreviations: AF; atrial fibrillation, ME; Middle Eastern, SA; South Asian

2.3.3.3. Management of AF

Rate control was the strategy reported in more than half of the patients. Rhythm control was approached in up to one-third of the patients with amiodarone use in up to 40% of them. Beta-blockers were used in more than 50% of the patients, digoxin in 30% and calcium channel blockers in approximately 20% of them. Only two AF registries [31,32] reported the use of ablation. In the Saudi registry (SAS) 3.8% of patients had been ablated [32]. The Iranian registry (IRAF) reported ablation use in 34.0% and 29.8% of patients with familial and non-familial AF, respectively [31]. The use of vitamin K antagonists (VKAs) across the studies ranged from about 40% to 70%, with more than 90% in two studies [34,41]. Of the 14 studies [17,20,24,26,31,32,34,35,40,41,43,44,46,59] that reported anticoagulation agents use, seven studies [20,31,35,40,41,43,44] recruited patients in the non-vitamin K oral anticoagulants (NOACs) era i.e., beyond 2010. Of the seven studies, two did not report NOACs use [20,35], four South Asian AF registries [40,41,43,44] reported use between 1.9% to 9.1%, and the IRAF registry reported higher average NOACs than VKAs use (45.7% versus 23.0%) [31]. Across the AF registries, aspirin and clopidogrel use ranged from 19.5% to 54.4% and 11.0% to 19.5%, respectively.

Table 5 Management in AF patients

Medication/strategy	**AF registries**		
	ME region		**SA region**
	Baseline medications [55]	In-hospital [32,59]	Baseline medication
Medication			
Beta-blocker	58.3%	66.0%	21.0 – 38.5%
Calcium channel blocker	16.3%%	20.8%	15.0 – 24.9%
Digoxin	36.1%	30.3%	22.2 – 31.9%
Amiodarone	9.2%	9.0 – 42.3%	7.4 – 37.2%
Other antiarrhythmics	3.1%	4.0 – 57.7%	0.8 – 33.0%
Antithrombotic agent			

Vitamin K antagonists	51.9%	38.5%	40.0 – 90.0%
NOACs	-	-	1.9 – 9.1%
Aspirin	54.4%	35.5%	19.5 – 23.0%
Clopidogrel	11.0%	1.5%	13.1 – 19.5%
Strategy			
Rate control	-	65.0 – 66.2%	46.1 – 87.8%
Rhythm control	-	12.0 -22.0%	12.2 – 35.2%
Ablation	-	3.8%	-

Abbreviations: AF; atrial fibrillation, ME; Middle Eastern, NOACs; non-vitamin K oral anticoagulants, SA; South Asian

2.3.4. Outcomes in AF

The main adverse outcomes reported by the studies included mortality (in-hospital, one-year), cerebrovascular events, and bleeding. In-hospital mortality was reported in 0.79% of patients in Bahrain [13] and was doubled in Thailand (1.6%) [37]. The rate was 3.6% in Qatar among patients admitted with general cardiac conditions [30], with a rate of 4.8% in Middle Eastern and 1.2% in South Asian patients as defined in the study [47], The rates were higher in patients with acute heart failure (6.7%) [26], chronic kidney disease (CKD) (11.7%) [51], ACS (14.7%) [27], and acute ischemic stroke (9.0% [20] and 26.8% [36]). One-year mortality rate ranged from 6.5% to 18.1% in four South Asian studies [37,40,43,44]. Gulf SAFE registry reported a rate of 15.0% [58] with a significantly lower mortality rate in patients who were compliant with the AF Better Care (ABC) pathway (7.3% versus 13.1%, P = 0.033) [55]. In the same registry, diabetic patients had significantly higher one-year mortality rate (14.4% versus 9.6%, P = 0.003) than non-diabetics [53]. Similarly, diabetic patients who were compliant with the ABC pathway had lower mortality rate as well (5.8% versus 15.9, P = 0.0014) [54]. Higher one-year mortality rates (> 20%) were reported in AF patients presenting with ACS [27] or acute heart failure [26]. The observed rate of cerebrovascular accident (CVA) and/or transient ischemic attach (TIA) in the South Asian AF registries ranged from 0.85% to 3.0% [43,44,60], while a single-centre study found much higher rates; 17.2% in non-valvular and 23.1% in valvular AF patients [35]. The Gulf SAFE reported a rate of 6.4% [58], while the Qatari registry reported a lower rate of 1.1% in patients admitted with cardiac condition [46]. The rate was

higher in Middle Eastern (1.4%) than South Asian (0.6%) populations [47]. The rates of CVA/TIA in special AF patient populations were 2.3%, 2.0%, 1.8 – 2.8%, and 6.7% in CKD [51], acute heart failure [26], AMI/ACS [27,48], and RHD [39], respectively. Two single-centre studies from Iran reported higher rates in patients presenting with AMI (12.5% [18] and 13.6% [15]). Finally, the rate of major bleeding in studies from the Middle East [26,27,58] ranged from 1.1% to 1.7% including those in patients presenting with ACS [27] and acute heart failure [26]. However, one-single centre study from KSA reported a rate of 35.6% in those with high risk of bleeding [7]. Studies from South Asia reported rates ranged from 0.31% to 4.4% [35,43,44,60]. A study from UAE found that the use of inappropriate NOACs doses subjected the patients to higher ischemic stroke and major bleeding rates compared to those on appropriate doses (9.9% versus 3.1%, P <0.01 and 11.7% versus 6.0%, P = 0.04; respectively) [8].

2.3.4.1. Risk determinants of AF

In hypertensive Thai patients, older age, male gender, and presence of CKD increased the prevalence of AF. On a multivariate analysis, factors of strongest association with increased prevalence were age of 65 years or above (adjusted odd ratio (adj OR) 2.86, 95% confidence interval (CI), 1.89 – 4.33; P <0.001) followed by male gender (adj OR, 1.98, 95%CI, 1.35 – 2.91; P <0.01), lower low-density lipoprotein-cholesterol (adj OR, 1.87, 95%CI, 1.28 – 2.73; P <0.01) and high uric acid levels (adj OR, 1.48, 95%CI, 1.02 – 2.17; P <0.05). The presence of combined factors, further increased the risk. Odds increased from 2.46 (95%CI, 1.66 – 3.63; P <0.001) with two factors to 8.99 (95%CI, 5.02 – 16.07; P <0.001) with the four factors combined [38]. In Indian patients with RHD, the following variables were independent determinants of AF, age (adj OR, 1.04, 95%CI, 1.03 – 1.06), mitral stenosis (MS) (moderate MS (adj OR, 2.4, 95%CI, 1.7 – 3.4) or severe MS (adj OR, 2.1, 95%CI, 1.5 – 3.0)), left atrial size (adj OR 1.10, 95%CI, 1.08 – 1.11), New York Heart Association classes (II, III, IV), all

degrees of tricuspid regurgitation (TR), and combined mitral regurgitation and MS with or without TR [39]. In patients hospitalized with AMI, the only independent factor of AF was age (adj OR, 1.06, 95%CI, 1.04 – 1.08; P = 0.001) in the Qatari registry [48].

2.3.4.2. Risk determinants of outcomes in AF

In the Qatari registry, ACS was associated with increased risk of in-hospital mortality (adj OR, 4.36, 95%CI, 1.77 – 10.74; P = 0.001) [30][47] but not age alone as predictor of mortality. Beta-blocker administration upon hospital admission was a good predictor for reduced in-hospital mortality (adj OR 0.36, 95%CI, 0.15 – 0.87; P = 0.02) in a multiple logistic regression analysis [30]. In the same registry, gender [46] or ethnicity [47] was not associated with poor outcomes. Multivariate analysis found the following as predictors of in-hospital mortality, cardiogenic shock (adj OR, 285, 95%CI, 84.0 – 970; P = 0.001), diabetes mellitus (adj OR, 1.52, 95%CI, 1.03 – 2.26; P = 0.04), and chronic renal impairment (adj OR, 1.18 – 3.68; P = 0.001) [46]. In Thailand, predictors of mortality after AF hospitalization included CKD (hazard ratio (HR), 2.01, 95%CI, 1.68 – 2.41; P <0.0001), high CHA2DS2-VASc score (e.g., ≥6; HR, 2.23, 95%CI, 1.34 – 3.70; P <0.002), and RHD (HR, 1.72, 95%CI, 1.53 – 1.92; P <0.0001) [37]. In Thai patients who experienced AF-associated acute ischemic stroke on admission or during hospitalization, age (≥ 75 year) and acute kidney injury were independent risk factors for three-month mortality (adj OR, 3.08, 95%CI, 1.17 - 8.13; P = 0.019 and adj OR, 6.38, 95%CI, 1.96 - 20.76; P = 0.001, respectively). Baseline oral anticoagulation therapy was associated with 87% risk reduction (adj OR, 0.13, 95% CI, 0.03 - 0.64; P = 0.002) [36].

In the Gulf SAFE registry, in-hospital or emergency room (ER) mortality were strongly associated with congestive heart failure (adj OR, 2.64, 95%CI, 1.79 – 3.89; P <0.001), peripheral vascular disease (adj OR, 2.26, 95%CI, 1.01 – 5.08; P = 0.048), and reason for ER visit (cardiac and noncardiac). Warfarin and antiplatelet use upon discharge were independent

protective factors (adj OR, 0.51, 95%CI, 0.32 – 0.83; P = 0.006 and adj OR, 0.55, 95%CI, 0.35 – 0.87; P = 0.01, respectively) [59]. When comparing patients with and without diabetes mellitus, in-hospital or ER mortality was associated with only CKD (relative risk (RR) 6.38, 95%CI 2.73–14.87) in diabetic patients. Whereas, in non-diabetics, several factors were involved, age ≥ 75 years (RR, 3.04, 95%CI, 1.69 – 5.50), CKD (RR, 7.41, 95%CI, 3.69 – 14.92), heart failure (RR, 2.05, 95%CI, 1.21 – 3.68), and stroke (RR, 3.00, 95%CI, 1.51 – 5.98). Predictors of one-year mortality in both diabetics and non-diabetics were older age (≥ 75 year), heart failure, and CKD. Digoxin use increased mortality risk by 74% in the absence of diabetes (RR, 1.74%, 95%CI, 1.04 – 2.90; P = 0.035). In contrast, 55% mortality risk reduction was associated with beta-blocker use in diabetic patients (RR, 0.45, 95%CI, 0.24 – 0.84; P = 0.012) [53]. History of previous stroke or TIA increased the risk of one-year stroke event rate (OR, 2.81, 95%CI, 1.82–5.00; P = 0.001). Similarly, antithrombotic therapy (ATT) undertreatment (OR, 2.76, 95% CI, 1.42 – 5.35; P = 0.003) but not ATT overtreatment, was associated with one-year stroke risk. However, ATT overtreatment was the only factor associated with significantly higher one-year major bleeding event rate (OR, 3.29, 95%CI, 1.51 – 7.15; P = 0.003) [57]. In patients with non-valvular AF, smoking, cardiac reasons for ER visit, and both CHADS2 and CHA2DS2-VASc scores of ≥2 were independent predictors of one-year stroke or TIA. Warfarin prescription upon discharge reduced the risk by about 60% (OR, 0.38, 95%CI, 0.17 - 0.83; P = 0.015) [59]. Adherence to the ABC pathway was significantly associated with lower six-month and one-year mortality either in the entire registry population (OR, 0.31, 95%CI, 0.13 – 0.77; P = 0.013 and OR, 0.46, 95%CI, 0.25 – 0.86; P = 0.015, respectively) [55], or in diabetic population (OR, 0.18, 95%CI, 0.42 - 0.75; P = 0.019 and OR, 0.29, 95%Cl, 0.11 - 0.76; P = 0.012, respectively) as compared to the non-ABC adherent group [54].

2.3.5. International registries

Middle-Eastern Arabs and South Asians were included as part of five AF international registries [62-66] (Table 6). The age of patients (i.e., range 57.9 – 70.0 years) and female distribution (i.e., range 41.0 – 57.6%) were in the ranges reported in the registries of this review. The South Asian registries reported wider variabilities in the rate of heart failure, hypertension and diabetes, but not stroke, compared to those in the Middle-Eastern ones. The rates of those co-morbidities were similar to those in the international registries except for stroke in the RE-LY AF registry [RE-LY-AF] which reported a higher rate in the Middle East. RHD was the highest in India (31.5%) [62]. Similarly, there was wide range in the rates of AF types in the South Asian registries. The rates of paroxysmal and permanent AF were higher in the international registries. It is important to mention that the regions and distribution of countries in the international registries were different from the WHO regions. The RE-LY AF registry [62] concluded with large regional variations in age, co-morbidities, risk factors, and management. Substantial regional differences in stroke prevention have been found in the GLORIA-AF registry during phase II with oral anticoagulation use rate of 87.4% in Africa/Middle East [63], which is higher than the rate reported in this review (i.e., range 38.5 – 51.9%).

Table 6 Patient characteristics in international registries

	GARFIELD-AF	GLORIA-AF phase I	GLORIA-AF phase II	RealiseAF	RE-LY AF
Sample size	39898	1063	15092	10523	15400
Relevant region (Countries involved)	**Asia** (Singapore, China, Japan, South Korea, Thailand and India) **Others** (Australia, Egypt, South Africa, UAE)	**ME** (Egypt, Lebanon, Turkey, UAE)	**Africa and ME** (KSA, Lebanon, South Africa, UAE)	**Asia** (Azerbaijan, India, Taiwan, Turkey) **ME and Africa** (Algeria, Egypt, Lebanon, Morocco, Tunisia)	**India** **ME** (Egypt, Iran, KSA, Turkey, UAE)
Results presentation	**Asia/Others**	**ME**	**Africa-ME**	**Asia/Africa-ME**	**India/ME**
Region size (%)	11117 (27.8%)/ 1227 (3.0%)	59 (5.6%)	597 (4.0%)	1703 (16.1%)/ 1680 (15.9%)	2536 (16.4%)/ 887 (5.7%)
Enrolment period	Mar 2010 to Sept 2015	May 2011 to Jan 2013	Nov 2011 to Dec 2014	Oct 2009 to May 2010	Sept 2008 to April 2011
Age (year)	67.4/68.5	65.0	70.0	66.4/61.1	57.9/58.6
Female sex (%)	41.0/42.2%	57.6%	47.6%	46.0/54.2%	50.3/43.6%
Heart failure	19.8/17.8%	25.4%	30.3%	-	17.7/28.4%
Hypertension	68.4/76.6%	79.7%	80.4%	67.5/54.7%	41.6/56.1%
Diabetes mellitus	21.7/23%	37.5%	42.2%	24.9/22.7%	20.2/36.2%
Prior stroke	10.8/16.5%	10.2%	18.1%	-	7.4/22.1%
CAD/IHD	CAD: 17.5/26.2% ACS: 7.2/16.2%	CAD: 27.4% MI: 13.6%	CAD: 32.5% MI: 16.6%	CAD: 32.8/19.1%	MI: 15.5/17.2%
VHD	-	-	-	38.6/31.5%	-
RHD	-	-	-	-	31.1/15.3%
Smoking	12.8/10.4%	-	-	10.0/13.7%	-
HAS-BLED	1.4/1.6	-	-	-	-
CH_2ADS_2-VASc	2.9/3.3	-	-	-	-
HAS-BLED ≥ 3	-	16.9%	10.2%	-	-
$CHADS_2 \geq 2$	-	61.0%	-	-	-
CH_2ADS_2-VASc ≥ 2	-	89.8%	89.8%	-	-
New onset	-	-	-	7.8/10.7%	-
Paroxysmal	-	67.8%	47.9%	26.1/17.2%	20.5/20.8%
Persistent	-	22.0%	31.8%	17.9/21.6%	32.9/7.5%
Permanent	-	10.2%	20.3%	48.2/50.5%	46.6/71.7%
Amiodarone	-	-		-	10.0/3.5%

Abbreviations: ACS, acute coronary syndrome; CAD, coronary artery disease; IHD, ischemic heart disease; KSA, kingdom of Saudi Arabia; ME, Middle East; MI, myocardial infarction; NOACs, non-vitamin K oral anticoagulants; RHD, rheumatic heart disease; UAE, United Arab Emirates; VHD, valvular heart disease. References: GARFIELD-AF [65], GLORIA I [64], GLORIA II [63], RealiseAF [66], RE-LY [62]

2.4. Literature Gaps identified and future research directions

Our study identified several gaps in AF literature related to Middle-Eastern Arabs and South Asians. Importantly most of the available evidence is based on studies in the hospital setting with paucity of informative community-based or population-based studies representative of these two ethnicities/races. This is particularly important in correctly identifying the AF disease prevalence and burden. Socio-economic difficulties are an important barrier for conduct of these types of studies but can be overcome by joining internationally funded studies with samples of these and other ethnicities representative of the population. Furthermore, studies that address ethnic/racial in-equality and access to treatment, particularly OAC and the effects on outcomes, are lacking and should be baldly addressed in populations with mixed ethnicities and races including Middle-Eastern Arabs and South Asians. In addition, how ethnicity and race affect AF presentation symptomatology and interpretation needs to be examined.

2.5. Limitations

Although our study was conducted using rigorous research methodology; however, it is possible that some articles were not identified by our search. Additionally, excluded papers could contribute to potential bias in our results. The impact of these exclusions is unknown. Moreover, the gap in time between our search and completing our synthesis has definitely resulted miss recently published papers. However, we believe that this limitation is balanced by the meticulousness of our methodology and the included literature.

2.6. Literature Review Conclusions

Although in this scoping study we identified and summarized studies addressing clinical features and management of AF in Middle-Eastern Arabs and South Asians, however, the main body of evidence comes from hospital-based studies and is very limited and is considered incomplete. There is an evidence gap of knowledge of AF burden in these two ethnicities/races

that should be addressed in representative community or population-based studies. Our study highlights the need to further examine the effects of ethnicity and race in heart disease particularly in AF.

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3. IMPACT OF PUBLISHED WORK

This chapter summarized the individual publications in terms of novelty, main findings and significance. The summary paper was published in the cardiology journal ``Heart Views``; the official journal of the *Gulf Heart Association.*

3.1. Summary article citation

Salam AM. Atrial Fibrillation in Middle Eastern Arabs and South Asians: Summary of Published Articles in the Arabian Gulf. Heart Views. 2019 Oct-Dec;20(4):158-165. doi: 10.4103/HEARTVIEWS.HEARTVIEWS_116_19. Epub 2019 Nov 14. PMID: 31803372; PMCID: PMC6881872.

3.2. Introduction

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice accounting for approximately one-third of hospitalizations for cardiac rhythm disturbances [1-3]. AF is associated with increased risk for stroke, heart failure and death. The global burden of AF estimated at around 33.5 million with progressive increases in incidence, prevalence and AF-related mortality having major implications for healthcare costs and public health policy.

The epidemiology and clinical features of AF have primarily been characterized in whites of European-descent and while there are recognized ethnic differences in cardiovascular risk profiles [4], the world literature on the epidemiology of AF among different ethnicities is limited [5-9]. Moreover, most of the published reports of AF in non-white ethnicities have focused mainly on black (African-American) patients. Data about AF in Arabic and South-Asian populations is much more limited.

In the research summarized herein, I attempted to examine different aspects of AF, including: aetiologies; cardiovascular risk factors; therapy; and outcome in two unique ethnicities that

have not been adequately studied together previously (Middle Eastern Arabs and South Asians), using data from a national registry of cardiovascular diseases in a Middle Eastern country over a 20-years period. The research undertaken focused on several other aspects peculiar to the effects of AF in these two ethnicities. This included; religious fasting, gender differences, in patients with chronic kidney disease and acute myocardial infarction.

Qatar is a small Arab country with a population of around 600,000 (2001 Census) and 1, 6 million (2010 Census), consisting of Qatari and other Middle-eastern Arabs (less than 40%) as well as other ethnic groups. The vast majority of non-Arabs are South Asians mainly from India, Pakistan, Nepal and Bangladesh. The studies are based at Hamad General Hospital, Doha, Qatar. This hospital provides inpatient and outpatient medical and surgical care for the residents of Qatar; nationals and expatriates where more than 95% of cardiac patients are being treated in the country making an ideal centre for population-based studies. The vast majority of patients with acute cardiac conditions (>95%) are admitted to this hospital. Since the last decade of the 20th century, cardiovascular diseases are the leading causes of morbidity and mortality in the country.

The Cardiology and Cardiovascular Surgery Database at Hamad General Hospital was used for these studies. Data are entered on all patients admitted to Hamad General Hospital with cardiac illnesses. The investigation was approved by Hamad Medical Review Board prior to data analysis. Data were collected from the clinical records written by physicians at the time of patient's discharge from the hospital according to predefined criteria for each data point. These records have been coded and registered at the cardiology department since January 1991.

With the described database, all patients presenting with AF requiring hospitalization in the 20-year period between 1991 and end of 2010 were retrospectively identified and data examined.

3.3. Studies Novelty, Main Findings and Significance

3.3.1. Secular Trends, Treatment and Outcome of Middle-eastern Arab and South Asian Patients Hospitalized with Atrial Fibrillation

3.3.1.1. FULL CITATION:

Salam AM, AlBinali HA, Al-Mulla AW, Singh R, Al Suwaidi J. Secular trends, treatments, and outcomes of Middle Eastern Arab and South Asian patients hospitalized with atrial fibrillation: insights from a 20-year registry in Qatar (1991-2010). Angiology. 2013 Oct;64(7):498-504. doi: 10.1177/0003319712460332. PubMed PMID: 23028177.

3.3.1.2. NOVELTY

Most of the medical research has focused on the prevalence and incidence of AF in different populations and countries [1-3]. However, the literature is scarce in studies addressing secular trends in the incidence and subsequent mortality in a contemporary, nationally representative sample of different ethnicities [3,9]. The literature is particularly devoid from studies addressing that in Middle Eastern Arab and South Asian ethnicities which this study examined over a 20-year period.

3.3.1.3. MAIN FINDINGS

During the 20-years period; 2857 Arabs and 548 Asians were hospitalized for AF. Arabs were 9 years older (58 vs. 49, $p<0.001$), with higher prevalence of hypertension (41.7% vs. 28.8%, $p<0.001$) and diabetes mellitus (37.5% vs. 25.7%, $p<0.001$), compared to Asians. Valvular heart disease and acute coronary syndromes were more common among Asians (6.8% vs.3.7%;

p<0.001, and 9.9% vs. 6.9%; p=0.02, respectively), while congestive heart failure was more common in Arabs (20% vs.12.4%, p<0.001). Overall, in-hospital mortality was lower for Asians compared to Arabs (2.6% vs.4.8%, p=0.02), while stroke rates were comparable. There were significant variations in the prevalence of underlying cardiac aetiologies in both ethnicities, with an increase in ischemic heart disease and decrease in the prevalence of valvular heart disease in the latter years of the study but mortality trend was steady in both ethnic groups over the study period. There was an increase in the prevalence of diabetes mellitus and hypertension in both groups in the latter years of the study period compared to earlier years but there was no change in mortality trends. There was a significant increase in the use of anticoagulants over the 20 years period from 17 % to 44.1% in the overall cohort. Ethnicity was not an independent predictor of higher mortality when corrected for other predictors by Multivariate analysis.

3.3.1.4. SIGNIFICANCE

Previous studies have suggested that the mortality and morbidity associated with AF was not homogeneous when taking into consideration underlying aetiologies, related co-morbidities, complications, and treatment strategies. Given the improvements in the recognition and management of the co-morbid conditions associated with AF, especially hypertension, heart failure, and coronary artery disease, one would expect an improvement in the clinical outcome and prognosis [10,11]. This was not the case as demonstrated by the steady rate of mortality and stroke over the 20 years of our study, although our analysis was limited to in hospital outcomes.

In addition, our study also highlights the suboptimal use of oral anticoagulation in patients with AF in spite of convincing evidence from large randomized trials showing that anticoagulation significantly reduces stroke rates in patients with AF. To the best of our knowledge the current

study was the first ever report of comparative ethnic trends in aetiologies and outcome of AF over a 20-year period.

3.3.2. Women Hospitalized with Atrial Fibrillation: Gender Differences, Trends and Outcome

3.3.2.1. FULL CITATION:

Salam AM, AlBinali HA, Al-Mulla AW, Asaad N, Singh R, Al-Qahtani A, Al Suwaidi J. Women hospitalized with atrial fibrillation: gender differences, trends and outcome from a 20-year registry in a Middle Eastern country (1991-2010). Int J Cardiol. 2013 Sep 30;168(2):975-80. doi: 10.1016/j.ijcard.2012.10.041. PubMed PMID: 23159409.

3.3.2.2. NOVELTY

While there are an increasing number of studies addressing the issue of gender differences in cardiovascular disorders particularly coronary artery disease [12], nonetheless, only few studies have dealt with gender differences and AF [13-16]. Some studies suggested less favourable outcomes in women with higher relative mortality, a higher risk of stroke and an underuse of anticoagulants [15-17]. However, results from these studies were inconsistent and included relatively small numbers of women over a short time period. Moreover, most of published studies were conducted in the developed world and included mainly Caucasian patients. Data about women with AF among other ethnicities are very limited. The current study extended these observations in two unique ethnicities that have not been adequately studied previously; (Middle Eastern Arabs and South Asians), and reported for the first-time secular trends of patients hospitalized with AF according to gender over a 20-years period.

3.3.2.3. MAIN FINDINGS

During the 20-years period; 1417 women and 2432 men were hospitalized for AF. Women were 5 years older (59 vs. 54, $p<0.001$) and more likely to have diabetes mellitus (37.5% vs. 25.7%, $p<0.001$) and hypertension (49.5% vs. 32.1%, $p<0.001$), and were also less likely to be current smokers (1.3% vs. 18.9%, $p<0.001$), and to have ischemic heart disease (8.3% vs. 12.3, $p<0.001$), when compared to men. There was no gender preference in the use of anticoagulation. The prevalence of concomitant ischemic heart disease and hypertension increased, while the prevalence of valvular heart disease and heart failure decreased among patients hospitalized with AF over the study period. In-hospital mortality and stroke rates were not different between the two groups. The use of warfarin was significantly trending higher over the study period but no differences were found between men and women. Multivariate predictors of poor outcome among patients hospitalized with AF are age, diabetes mellitus and chronic renal impairment. Gender was not an independent predictor of poor outcome.

3.3.2.4. SIGNIFICANCE

Healthcare in the third world countries have long been accused of being biased against women [18] particularly in the use of evidence-based treatment and consequently higher morbidity and mortality in women even when other risk factors are accounted for. The major evidence-based treatment in AF is stroke prevention therapy and our study showed equal use of anticoagulants and anti-platelets among both sexes in our patients. In addition, after correcting for other risk factors, female gender was not independently associated with poor outcome. Furthermore, the prevalence of diabetes mellitus was much higher than any previous reports. This is consistent with the high prevalence of diabetes mellitus in the Arab Middle east in general and in Qatar specifically [19] and may in part explain the relatively younger age of AF female patients among both Asian and Middle Eastern Arabs.

3.3.3. Effect of Age on Treatment, Trends and Outcome of Patients Hospitalized With Atrial Fibrillation

3.3.3.1. FULL CITATION

Salam AM, AlBinali HA, Al-Sulaiti EM, Al-Mulla AW, Singh R, Al Suwaidi J. Effect of age on treatment, trends and outcome of patients hospitalized with atrial fibrillation: insights from a 20-years registry in a Middle-Eastern country (1991-2010). Aging Clin Exp Res. 2012 Dec;24(6):682-90. doi: 10.3275/8757. PubMed PMID: 23211770.

3.3.3.2. NOVELTY

It has long been established that AF is a disease of aging with AF incidence doubling with each decade of life [20]. Studies have estimated that the annual incidence of AF per 1000 person-years to be 1.9 in women and 3.1 in men younger than 65 years, but exceeds 32 per 1000 person-years in patients 80 years and older. Age-related declines in vascular compliance, increased population longevity, and the increasing prevalence of cardiovascular disease in older persons has led to an expanding AF epidemic in the developed world [21-25]. However, most studies on AF epidemiology, treatment, and outcomes have been performed in North America and Europe involving mainly Caucasian patients and while there are recognized ethnic differences in cardiovascular risk profiles, the world literature on epidemiology of AF in different ethnicities is limited, particularly concerning elderly patients. Herein we studied the presentation, treatment and outcome of elderly patients aged above 70 years that were hospitalized with AF and compared them to younger age groups in a population of Middle Eastern Arabs and South Asians over a 20-years period.

3.3.3.3. MAIN FINDINGS

1345 patients were ≤50 years, 1759 were between >50 and 70 years and 744 patients were >70 years old. Elderly patients were more likely to have hypertension and chronic renal impairment. There was a higher prevalence of associated coronary artery disease and aortic stenosis in elderly patients with a lower left ventricular ejection fraction than the younger age groups. A lower use of anticoagulation in the elderly group was observed but there was no underuse of other evidence-based medications. The older age AF patients had significantly higher in-hospital mortality and stroke rates with no significant changes in mortality trends over the 20-years of study. Secular trends analysis showed that the associated acute coronary syndromes, hypertension and diabetes mellitus prevalence were trending higher in the elderly group while heart failure prevalence was trending lower. There were no significant differences in mortality trends in the elderly group while stroke rate was higher. The use of warfarin as well as aspirin in the elderly group was significantly trending higher over the study period. Multivariate analysis of mortality predictors showed that increasing age was not an independent predictor of in-hospital mortality.

3.3.3.4. SIGNIFICANCE

We report under-utilization of oral anticoagulants (OAC) in the elderly group in our patient population. This is quite alarming considering the overwhelming evidence supporting OAC for stroke prevention [26]. Nonetheless, the use of warfarin in the elderly group was significantly trending higher over the study period reflecting perhaps increasing awareness among treating physicians of its importance and indication. We have not studied the reasons behind under-utilization of OAC in our group but reported reasons include physicians` underestimation to risk of stroke, overestimation of the risk of haemorrhagic complications, the frailty of elderly people, cognitive impairment, poor compliance of monitoring, falls risk, associated co-

morbidity and concomitant medications which may, indeed, play a role in our observations. The current study underscores the urgent need for prospective studies to investigate warfarin contraindications, relative warfarin efficacy and bleeding risks in our region to help guide healthcare providers in warfarin prescribing in this frail patient population and consequently reduce the risk of AF-related disabling strokes and mortality.

3.3.4. The Prognostic Implications of Lack of Palpitations in Patients Hospitalized with Atrial Fibrillation

3.3.4.1. FULL CITATION

Salam AM, Gersh BJ, AlBinali HA, Singh R, Asaad N, Al-Qahtani A, Suwaidi JA. The prognostic implications of lack of palpitations in patients hospitalised with atrial fibrillation: observations from a 20-year registry. Int J Clin Pract. 2014 Jan;68(1):122-9. doi: 10.1111/ijcp.12230. PubMed PMID: 24341306.

3.3.4.2. NOVELTY

It is well recognized that the presentations of AF at the time of first diagnosis vary substantially with palpitations being the most common typical symptom. Other atypical symptoms include chest pain, shortness of breath (SOB) and dizziness [27]. In addition, about 15% to 30% of patients are asymptomatic [28-31]. It is sometimes practiced that when AF is thought to be suppressed, as evidenced by the absence of clinical symptoms and the presence of sinus rhythm on routine electrocardiograms, some physicians tend to stop anticoagulation in an effort to avoid the perceived unnecessary exposure of patients to anticoagulation therapy [32]. Nonetheless, evidence from ambulatory external electrocardiogram monitoring and examining implanted device memories have demonstrated that such patients may have asymptomatic

recurrences of AF and that these subclinical episodes expose them to the risk of ischemic stroke and other thromboembolic events [33-35], thereby questioning the utility of lack of symptoms as an indicator of lower risk. The aim of this study was to examine the prevalence and prognostic implications of lack of typical symptoms on presentation with AF, namely palpitations, among patients hospitalized with AF in a population of Middle Eastern Arabs and South Asians over a 20-years period.

3.3.4.3. MAIN FINDINGS

During the 20-years period, 3850 patients were hospitalized for AF; 1724 (44.8%) had palpitations on presentation while 2126 (55.2%) had no palpitations. Patients who lacked palpitations were 9 years older, had a higher prevalence of diabetes mellitus (64.7% vs. 35.3%), underlying coronary artery disease (14.6%, vs. 6.2%,) and severe left ventricular dysfunction on echocardiography (25.5% vs. 6.6%), (all, P value =0.001). There were 141 deaths among the group with no palpitations compared with 19 among the group with palpitations (6.6% versus 1.1%). Multivariate analysis of mortality predictors identified -lack of palpitations- as an independent predictor of in-hospital mortality (relative risk 5.56; 95% confidence interval 1.20 – 25.0, p= 0.03).

3.3.4.4. SIGNIFICANCE

The current study represents the largest observational study comparing the impact of symptoms at the presentation with AF on patient outcomes. The mortality rate of patients without palpitations was significantly higher compared to patients with palpitations. In addition, the study demonstrated for the first time that absence of palpitations was an independent predictor of in-hospital mortality. We suspect that this most likely could be due to confounders, which were significantly more frequent in these patients so that in patients who were admitted in acute coronary syndromes (ACS) or heart failure, the presence of other more severe symptoms may

have overshadowed the presence of milder symptoms of palpitations. Yet To the best of our knowledge the study was the first ever report demonstrating that -lack of palpitations- as predictor of mortality independent of other risk factors or therapy. Further research is warranted to confirm and explain the mechanisms behind this novel observation and to investigate the utility of this cost-effective prognostic indicator in risk stratification of patients with AF.

3.3.5. Impact of chronic kidney disease on the presentation and outcome of patients hospitalized with atrial fibrillation

3.3.5.1. FULL CITATION

Salim I, Al Suwaidi J, AlBinali HA, Singh R, Al-Qahtani A, Asaad N, **Salam AM**. Impact of Chronic Kidney Disease on the Presentation and Outcome of Patients Hospitalized With Atrial Fibrillation: Insights From Qatar. Angiology. 2018 Mar;69(3):212-219. doi: 10.1177/0003319717717849. PubMed PMID: 28691505.

3.3.5.2. NOVELTY

Patients with Chronic Kidney Disease (CKD) have a high prevalence of cardiovascular disorders (CVD) which is responsible for most of the morbidity and mortality associated with CKD rather than progression to end stage renal failure [36,37]. Furthermore, most of the available literature describe AF in cohorts of patients with CKD showing high prevalence and incidence and associated higher morbidity and mortality [38-42]. Yet, the clinical characteristics and outcome of patients who are hospitalized with AF and coexistent CKD have rarely been reported. In this study, we examined the clinical presentation, management and outcomes of patients hospitalized with AF, with and without co-existent CKD, in a population of Middle Eastern Arabs and South Asians over a 20-years period.

3.3.5.3. MAIN FINDINGS

Out of 5201 AF patients; 264 (5.1%) had CKD. Compared with patients without CKD, CV risk factors were significantly more prevalent in CKD patients including hypertension, diabetes mellitus (DM), and old myocardial infarction whereas smoking was more prevalent in patients with normal renal function. Patients with CKD were significantly more likely to present with shortness of breath and chest pain compared with patients without CKD. Palpitation was significantly more common in patients with normal renal function. Other cardiac diagnosis at the time of admission including ACS and heart failure were significantly more prevalent in CKD patients while there was no difference in valvular heart disease (p=0.6). In patients who underwent echocardiography, left ventricular (LV) dysfunction was significantly more frequent in patients with CKD while normal LV ejection fraction was significantly more frequent in patients with normal renal function. In-hospital stay (mean ± SD) was significantly longer for patients with CKD compared with patients without CKD (6.3±4.3 vs 4.5±3.6 days, p=0.001). Compared with patients without CKD, patients with CKD had significantly higher crude in-hospital mortality (11.7 vs 4.0%, p=0.001) and stroke (2.3- vs 0.3%, p=0.001). On multivariate analysis, independent predictors of in-hospital mortality were: CKD [Odds Ratio (OR) 2.84; 95% confidence interval (CI) 1.33 to 6.08, p=0.001], ACS [OR 2.97 (95% CI 1.67 to 5.30, p=0.001)], left ventricular ejection fraction (LVEF) ≤ 40% [OR 2.44; 95% CI 1.41-4.35, p=0.001] and DM [OR 1.96; 95% CI 1.03-3.70, p=0.04].

3.3.5.4. SIGNIFICANCE

The current study demonstrated that patients with CKD have different symptoms when presenting with AF compared to those with normal renal function. This finding suggests that these patients should be screened for the presence of AF particularly when the reason for

deterioration in not obvious, even in the absence of palpitations. Further research is required in order to reduce the high morbidity and mortality observed in this high-risk group.

3.3.6. Atrial Fibrillation in Middle-eastern Arab and South Asian Patients Hospitalized with Acute Myocardial Infarction

3.3.6.1. FULL CITATION

Salam AM, Al BH, Singh R, Gehani A, Asaad N, Al-Qahtani A, Suwaidi JA. Atrial fibrillation in Middle Eastern Arab and South Asian patients hospitalized with acute myocardial infarction: experience from a 20-year registry in Qatar (1991-2010). Acta Cardiol. 2013 Apr;68(2):173-80. PubMed PMID: 23705560.

3.3.6.2. NOVELTY

AF has been reported to complicate the course of acute myocardial infarction (AMI) in about 6–21% of hospitalized patients [43,44]. There is increasing evidence that there are variations in the susceptibility and incidence of AF complicating AMI in different ethnicities [45,46]. However, most of the available literature is derived from trials and studies performed in North America and Europe while other parts of the world are under-represented in AF research.

Herein, we study the incidence, predictors of AF after AMI and prognostic implications of this arrhythmia on in-hospital AMI outcomes in two ethnicities that have not been adequately studied together previously (Middle Eastern Arabs and South Asians), in a Middle Eastern country over a 20-years period. Retrospective analysis of a prospective registry of all patients hospitalized with AMI in the State of Qatar from 1991 through 2010 was made. Clinical characteristics and outcomes of AMI patients with and without AF were compared. Sub-analysis according to ethnicity was also performed.

3.3.6.3. MAIN FINDINGS

During the 20-years period; a total of 12881 patients were hospitalized with AMI of these 5028 were Arabs and 5985 were South Asians. A total of 227 had AF during hospitalization with an overall incidence of 1.8% (156 Arabs; incidence 3.1% and 48 South Asians; incidence 0.8%). The mean age of AF patients was 65 years (Arabs 69, South Asians 54). Patients with AF were significantly older and had more cardiovascular co-morbidities compared to patients without AF, and were more likely to have non-ST elevation AMI on presentation. Patients with AF had significantly higher in-hospital mortality rate (20.3% versus 7.1%; P=0.001) and stroke rates (1.8% versus 0.3%; P=0.001) when compared to patients without AF. Age was the only independent predictor of AF development in patient with AMI in our study.

3.3.6.4. SIGNIFICANCE

We report an overall incidence of 1.8% of AF in our AMI patients which is lower than that observed in other studies performed in North America and Europe which showed an incidence ranging from 6% to 15% depending on the cohort of AMI studied [46,47]. Sub-analysis according to ethnicity revealed an incidence of 0.8% in South Asians. This very low frequency observed in South Asians is concordant with earlier observations in this ethnicity. We also report an incidence of 3.1% in Arabs in our cohort. This is consistent with our previous observation from the second Gulf Registry of Acute Coronary Events (Gulf RACE-2) analysis [48], which revealed an incidence of 2.7% of AF in a cohort of patients with acute coronary syndromes from six adjacent Arabian Gulf countries (Bahrain, Saudi Arabia, Qatar, Oman, United Arab Emirates, and Yemen) collected over 9 months. Increased age was actually the only predictor of AF in the current study. Considering that the mean age of our AMI cohort was 53 years, which is much lower than that in other registries and AMI studies, this may be the reason behind the very low rates of AF in our study. Our findings confirm previous reports

in other ethnicities that advancing age is the major independent predictor of AF in AMI patients [45,47]. Finally, our study demonstrated a significant impact of AF on survival in patients with AMI with increased in-hospital mortality and stroke rates.

3.3.7. Impact of Religious Fasting on the Burden of Atrial Fibrillation: A Population-Based Study

3.3.7.1. FULL CITATION

Salam AM, AlBinali HA, Salim I, Singh R, Asaad N, Al-Qahtani A, Al Suwaidi J. Impact of religious fasting on the burden of atrial fibrillation: a population-based study. Int J Cardiol. 2013 Oct 3;168(3):3042-3. doi: 10.1016/j.ijcard.2013.04.131. PubMed PMID: 23642825.

3.3.7.2. NOVELTY

Religious fasting is practiced by over one billion Muslims worldwide and represents a radical change in lifestyle for the period of one lunar month (Ramadan) [49]. How such prolonged fasting affects the burden of AF is unknown. Our objective in this study was to investigate whether Ramadan fasting had any effect on the number of hospitalizations with AF in a geographically-defined population. This study focused only on Middle Eastern (Qatari) patients rather than South Asians (expatriates) because it is a stable population and avoids the bias in the fluctuation of expatriate population in the country that varies from time to time. In addition, more than 95% of Qatari adults fast without fail during the month of Ramadan. All Qatari patients hospitalized with AF in Qatar from 1991 through 2010 were identified. Patients were divided according to the time of presentation in relation to the month of Ramadan; 1 month before, during and 1 month after Ramadan. The number of AF hospitalizations, clinical

characteristics and outcome were analysed in various time periods. We have used hospitalizations for AF as a reflection of AF incidence during the period of study.

3.3.7.3. MAIN FINDINGS

Overall, 1718 Qatari patients were hospitalized for AF during the 20-year period with a mean age of 61. The number of hospitalizations for AF was not significantly different in Ramadan (143 cases) when compared to a month before Ramadan (136 cases) and a month after Ramadan (151 cases); p = 0.95. The rate of hospitalizations of patients with underlying myocardial ischemia was significantly lower in Ramadan (9.8%) compared to other months (19.1% & 23.2%; P= 0.02).

3.3.7.4. SIGNIFICANCE

This population-based study demonstrated for the first time that fasting has neutral overall effects on AF hospitalizations and suggested a favourable protective effect from fasting on ischemic AF. We have previously studied other cardiovascular disorders in relation to fasting [50-52] including; acute coronary syndromes, heart failure and chronic ischemic heart disease. The current study complements these studies and addresses AF that was not previously studied.

There are two hypotheses for the reduction of ischemic AF burden during fasting. The first is that the favourable effects on lipid profile which we reported [53] during fasting provided protection from myocardial ischemia. The other hypothesis is related to the favourable effect of catecholamine inhibition that occurs during fasting. Hunger has been associated with catecholamine inhibition (catecholamine surge has been implicated as a trigger for acute coronary syndromes) and reduced venous return, causing a decrease in the sympathetic tone, which leads to a fall in blood pressure, heart rate and cardiac output [54,55].

3.4. Limitations

Studies were constrained by the limitations inherent in all studies of historical, observational design. Inaccuracies in the diagnosis and coding of AF in routine data are well recognized and we have of necessity relied on the accuracy of such data. Temporal changes in referral and coding practices, in diagnostic accuracy, and in awareness of AF as a diagnostic entity may have influenced our findings. Other limitations could include missing data or measurement errors, possible confounding by variables not controlled for, as these were observational studies. In addition, the studies focused on in-hospital outcome and long-term data is not available.

3.5. Conclusions

Despite any limitations, these studies shed light upon important aspects of AF presentations and outcomes in Middle Eastern Arab and South Asian ethnicities. In the process, several novel observations were reported and new questions were raised that warrant further investigations and further studies.

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4. INDIVIDUAL PAPERS

4.1. Secular trends, treatments, and outcomes of Middle Eastern Arab and South Asian patients hospitalized with atrial fibrillation: insights from a 20-year registry in Qatar (1991-2010)

4.1.1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice accounting for approximately one-third of hospitalizations for cardiac rhythm disturbances [1,2]. To date, most studies on AF epidemiology, treatment, and outcomes have been performed in North America and Europe involving mainly Caucasian patients [3,4] and while there are recognized ethnic differences in cardiovascular risk profiles [5], the world literature on the comparative epidemiology of AF between different ethnicities is limited (table 1) [6-14]. Moreover, most of the published reports of AF in non-white ethnicities have focused mainly on black (African-American) patients [15]. Data about AF in Arabic and South-Asian populations is much more limited.

Herein, we assess the prevalence; cardiovascular risk factors; therapy; and outcome of two unique ethnicities that have not been adequately studied together previously (Middle Eastern Arabs and South Asians), in a Middle Eastern country over a 20-years period.

Materials and methods

4.1.2. Study setting

Qatar is a small Arab country with a population of around 600,000 (2001 Census) and 1, 6 million (2010 Census), consisting of Qatari and other Middle-eastern Arabs (less than 40%) as well as other ethnic groups. The vast majority of Non-Arabs are South Asians mainly from

India, Pakistan, Nepal and Bangladesh [16,17]. This study is based at Hamad General Hospital, Doha, Qatar. This hospital provides inpatient and outpatient medical and surgical care for the residents of Qatar; nationals and expatriates where more than 95% of cardiac patients are being treated in the country making an ideal centre for population-based studies. The vast majority of patients with acute cardiac conditions (>95%) are admitted at this hospital. Since the last decade of the 20th century, cardiovascular diseases are the leading causes of morbidity and mortality in the country [16-20].

The Cardiology and Cardiovascular Surgery Database at Hamad General Hospital was used for this study. Data are entered on all patients admitted to Hamad General Hospital with cardiac illnesses. The investigation was approved by Hamad Medical Review Board prior to data analysis. Data were collected from the clinical records written by physicians at the time of patient's discharge from the hospital according to predefined criteria for each data point. These records have been coded and registered at the cardiology department since January 1991 [16-20].

With the described database, all patients presenting with AF requiring hospitalization in the 20-year period between 1991 and end of 2010 were retrospectively identified. Patients with AF were compared according to ethnicity.

The term Arab originally meant a member of the Semitic race of people of the Arabian Peninsula and currently refers to pan-ethnicity of people that live in the Arab world in the Middle-East. Patients from South Asia (countries of the Indian subcontinent namely; India, Pakistan, Nepal and Bangladesh) in our study will be referred to as Asians.

4.1.3. Definitions

AF was based on physician-assigned diagnoses and defined as the presence of AF on electrocardiogram (ECG): (characterized by the presence of an irregularly irregular rhythm with fibrillatory waves and no defined P-waves), during the index hospitalization [21]. Congestive heart failure (CHF) was defined using the Framingham criteria [22]. Acute myocardial infarction was defined for this study according to the World Heart Organization criteria [20]. Use of adjunct therapy during hospitalization was recorded for every patient. The presence of diabetes mellitus was determined by the documentation in the patient's previous or current medical record of a documented diagnosis of diabetes mellitus that had been treated with medications or insulin. The presence of hyperlipidaemia was determined by the demonstration of a fasting cholesterol > 5.2 mmol/L in the patient's medical record, or any history of treatment of hyperlipidaemia by the patient's physician [18]. Chronic renal impairment was defined as creatinine >1.5 upper normal range [23]. The presence of hypertension was determined by any documentation in the medical record of hypertension or if the patient was on treatment by the patient's physician. Smoking history: Patients were divided into current cigarette smokers, past smokers defined as more than 6 months abstinence from smoking, and those who never smoked.

4.1.4. Statistical Analysis

Patients' characteristics in the form of mean, SDs and frequency with percentages were expressed for interval and categorical variables respectively. The frequencies of categorical variables according to ethnicity were compared using the Chi-square tests and student t tests were used to compare continuous variables. Influential variables for in-hospital mortality were adjusted to see impact of ethnicity applying multivariate logistic regression with enter method. Adjusted Odds ratios (OR), 95% CI, and p values were reported. A p value less than equal to

0.05 was considered for statistical significant. All p values were the results of two-tailed tests. All data analyses were carried out using the Statistical Package for Social Sciences version 19.0 (SPSS Inc., USA).

4.1.5. Results

Overall, from the year 1991 to end of 2010, a total of 41,438 patients with acute cardiac disease were hospitalized. 3849 of patients were admitted with AF and 37589 patients were admitted with other cardiovascular diagnoses and no-AF. Among AF patients 3405 were eligible for this study; 2857 (83.9%) were Middle Eastern Arabs and 548 (16.1%) were South Asians. 444 patients were from other ethnicities and were excluded.

4.1.5.1. Baseline clinical characteristics (Table 2)

Arabs were 9 years older and more likely to have hypertension, diabetes mellitus, chronic renal impairment and dyslipidaemia compared to Asians. Valvular heart disease and acute coronary syndromes were more common among Asians while congestive heart failure was more common in Arabs. There was no significant difference in current smoking status, left ventricular function, or history of prior myocardial infarction between the two groups. Body mass index was less in Asians (27±6 versus 31±10, p = 0.001). The length of hospital stay was significantly longer among Arabs when compared to Asians.

4.1.5.2. Medications (Table 3)

At the time of admission; Arabs were more likely to be on aspirin, digoxin and antiarrhythmics, when compared to Asians. Beta-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACE/ARB), calcium channel blockers, warfarin and clopidogrel use was comparable between the two groups.

Admission: Arabs were more likely to be treated with digoxin and calcium channel blockers and less likely to be treated with beta-blockers and enoxaparin. There was no ethnic preference in the use of anticoagulation with Warfarin, nor there was a difference in the prescription of antiplatelets, ACE/ARB, antiarrhythmics or unfractionated heparin between the two groups.

Discharge: Arabs were more likely prescribed calcium channel blockers, antiarrhythmics and digoxin than Asians whereas warfarin and beta-blockers were significantly more prescribed to Asians. Antiplatelets and ACE/ARB were comparable between the two groups.

4.1.5.3. Outcomes and trends (Table 4)

In-hospital mortality was lower for Asians compared to Arabs while stroke rates were comparable. Over the 20-year period, patients hospitalized with AF in the latter period were 2 years older when compared to those hospitalized in the 1990s. Moreover, in the latter years, there was increase in the prevalence of diabetes mellitus and hypertension in both groups but more so in Arabs when compared to patients hospitalized in the earlier years.

Associated valvular heart disease was trending lower in both groups while ischemic heart disease prevalence was trending higher with no significant differences between the two groups. Rheumatic heart disease was statistically trending lower in prevalence, however it remained more prevalent among Asian patients over the study period. There were no significant differences in mortality or stroke trends over the study period between the two groups.

The use of warfarin was significantly trending higher over the study period but no differences were found between Arabs and Asians except at the latter years (2007-2010) when warfarin use was statistically higher in Asians (53% versus 41.1%, $p = 0.001$).

4.1.5.4. Predictors of in-hospital mortality (Table 5)

Multivariate predictors of poor outcome among patients hospitalized with AF are diabetes mellitus, chronic renal impairment and cardiogenic shock. Age and ethnicity were not independent predictors of poor outcome.

4.1.6. Discussion

The current study demonstrates for the first time 20-years observations of the clinical characteristics, treatment and outcome of patients hospitalized with AF according to ethnicity.

Arab patients were 9 years older and significantly more likely to have cardiovascular risk factors including hypertension, diabetes mellitus, dyslipidaemia, obesity and chronic renal impairment. Heart failure was also more common in Arabs while valvular heart disease was more common among Asians. The mortality of patients hospitalized for atrial fibrillation was lower in Asians compared to Arabs. Overall, the 20-years study period, there were significant variations in the prevalence of concomitant cardiac diseases in patients hospitalized with AF, with an increase in ischemic heart disease and decrease in the prevalence of valvular heart disease in the latter years of the study but mortality trend was steady in both ethnic groups over the study period.

4.1.6.1. Baseline Characteristics

Several studies reported clinical characteristics of patients hospitalized with AF, the vast majority of these studies were conducted in Europe and North America and included mainly patients of Caucasian ethnicity. Miyasaka and colleagues [3] reported 4618 patients with AF from Olmsted County, Minnesota, USA from 1980 to 2000.The mean age was 73.1 years. The most common co-morbid conditions were hypertension and coronary artery disease followed by valvular disease, heart failure and diabetes mellitus (80%, 38%, 24%, 19%, and 18%,

respectively). Other studies have shown consistent findings [2,5,8]. Compared to these studies from the developed world our Arab patients were more than 10 years younger with lower prevalence of hypertension (41%), and a higher prevalence of diabetes mellitus (34.6%). This high prevalence of DM is not limited to AF patients and was also observed among acute coronary syndrome [18] and heart failure [19] in Qatar.

Patients from the Indian subcontinent (which is comprised of the countries of India, Pakistan, Sri Lanka, Bangladesh, and Nepal), have a common ancestry and are referred to as "South Asians." South Asians represent one fourth of the world's population and have the highest proportion of cardiovascular disease CVD morbidity and mortality compared to other ethnicities [24]. Obesity, metabolic syndrome and diabetes are the major cardiovascular risk factors among South Asians [25] and the prevalence is on the rise which may, at least in part, account for the younger age of presentation with cardiovascular disease that is observed in these patients as was seen in our study. Additionally, studies have shown that compared with other ethnic groups, there is an increased prevalence of essential hypertension in South Asians [26]. How all these factors affect AF in this population is not well described, however. Our Asian group showed younger age of presentation with AF with a mean age of 49. Consistent with the literature of cardiovascular risk factors prevalence in this ethnic group, hypertension and DM were the most common aetiologies followed by CHF and Valvular heart disease (28.8%, 17.7%, 12.4, and 6.88% respectively).

Reasons for racial variation in AF are unclear but presumably include variations in genetic or environmental factors [27]. According to Ruo, "intrinsic racial differences in atrial membrane stability, atrial conduction pathways, or genetic polymorphisms [may] lead to different susceptibility" to AF development [28] Racial polymorphism differences have been associated with heart failure risk [29]. The Cardiovascular Health Study found racial differences in left

atrial size; average left atrial size was greater in elderly white males compared to blacks [30]. Furthermore, there may be racial differences in plasma or brain natriuretic peptide levels, both of which have been linked to AF development [31,32]. Additionally, mutations in genes coding channels (sodium and potassium), gap junction proteins, and signalling have been described, often in lone AF or familial AF series [33].

4.1.6.2. Treatment

Our study also highlights the suboptimal use of oral anticoagulation in patients with atrial fibrillation in spite of convincing evidence from large randomized trials showing that anticoagulation significantly reduces stroke rates in patients with AF [34]. Our findings in the earlier years of our study are consistent with results of studies conducted during the same period; a large study at that time by Stafford and Singer [35], using data from National Ambulatory Medical Care Surveys in the USA, showed that warfarin use in AF had improved from 7% in 1980 to 1981 to 32% in 1992 to 1993. Likewise, non-treatment declined from 90% to 48%. Interestingly, they showed that a trend of increasing warfarin use coincided with the publication of major landmark atrial fibrillation studies between 1989 and 1992 [36]. After that time Majeed and colleagues [37] study in general practice in England and Wales, reported the rate of warfarin use was low; 20% to 34% in men and 17% to 25% in women between 1994 and 1998. Our results are also concordant with the 23% found by Sudlow and colleagues in an earlier study from the north of England [38] and the 31% reported by Kalra and associates [39]. A higher treatment rate of 55% was reported by Go and colleagues in northern California during that period, however [40]. More recently the Euro Heart Survey on Atrial Fibrillation, reported higher prescription rate of oral anticoagulants (64.8%) [41].

Although the rate of patients who had contraindications to anticoagulation is unknown in the current study, previous investigators estimated that between 40–60% of patients might benefit

from anticoagulation [38, 42]. Nonetheless, our results are encouraging in that there was a significant increase in the use of anticoagulants over the 20 years period from 17 % to 44.1% in the overall cohort.

4.1.6.3. Outcomes and trends

Most of the medical research has focused on the prevalence and incidence of AF [6,8-14,37,38] however, to our knowledge; the literature is devoid from studies addressing secular trends in the incidence and subsequent mortality in a contemporary, nationally representative sample of different ethnicities similar to our study. Two studies from the USA stand out as an exception to this claim [2.3]; the first by Miyasaka and colleagues in an analysis from Olmsted County, Minnesota, where incident AF was associated with 23% mortality at 1 year [2,43]. In the second study, Piccini and colleagues [2] found similar risks, including a 1-year mortality rate of 27%. On the other hand, longer-term mortality in this Medicare population was lower than in the Olmstead County study (43% versus 63% at 3 years). These findings suggest that 1 in 4 older patients with AF will die within a year after the diagnosis.

Moreover, studies have suggested that the mortality and morbidity associated with AF was not homogeneous when taking into consideration related co-morbidities, complications, and treatment strategies. The presence of AF in patients with acute coronary syndromes, congestive cardiac failure, and in the post-operative setting condition was associated with greater risk of adverse events [44]. For example, an analysis from the TRAndolapril Cardiac Evaluation (TRACE) study reported AF to increase total mortality by 33%, with a risk ratio for sudden cardiac death (SCD) of 1.31 [45]. Similarly, results from the The EuroHeart Failure Survey [46] demonstrated new-onset AF was an independent predictor of in-hospital mortality in patients hospitalized with heart failure.

Given the improvements in the recognition and management of the co-morbid conditions associated with AF, especially hypertension, heart failure, and coronary artery disease, one would expect an improvement in the clinical outcome and prognosis. This was not the case as demonstrated by the steady rate of mortality and stroke over the 20 years of our study. Although our analysis was limited to in hospital outcomes, nonetheless our findings are consistent with the study by Miyasaka and colleagues [2,43] addressing longer term mortality. They reported that mortality risk was high, especially within the first 4 months, but more importantly; there was no evidence for any significant changes over the 21 years in terms of overall mortality, early or late mortality, or mortality among patients without pre-existing cardiovascular disease.

Further studies are urgently needed addressing different ethnicities and investigating the trends in cardiovascular profiles and therapeutic interventions and how they affect outcome in terms of morbidity and mortality in order to develop tailored strategies for the prevention of cardiovascular disease around the world.

4.1.7. Conclusion

The results of this 20-years observational study in residents of a Middle-Eastern country provide for the first-time insights into the characteristics, treatment practices, and in-hospital outcome among Middle-Eastern Arab and South Asians ethnicities. To the best of our knowledge the current study is the first ever report of comparative ethnic trends in aetiologies and outcome of AF over a 20-year period. The current study underscores the urgent need to study differences in atrial fibrillation among various ethnicities.

4.1.8. References

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4.1.9. Tables

4.1.9.1. Table 1. Studies addressing ethnic differences in atrial fibrillation

Table 7 Studies addressing ethnic differences in atrial fibrillation

Author	Study	Year published	Total Patients with AF	Caucasians (%)	Asians (%)	Hispanics or Latino (%)	African-American (%)	Middle-Eastern Arabs	Conclusions
Go et al [6]	Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study.	**2001**	**15 941**	**(84.7)**	--	**(2.5)**	**(3.6)**	--	Among persons aged 50 years or older, prevalence of atrial fibrillation was higher in whites than in blacks (2.2% vs 1.5%).
Ruo et al [7]	Racial Variation in the Prevalence of Atrial Fibrillation Among Patients With Heart Failure. The Epidemiology, Practice, Outcomes, and Costs of Heart Failure (EPOCH) Study	**2004**	**1,373**	**1,150**	--	--	**223**	--	Compared with Caucasians, African Americans were younger (mean age 67 vs. 74 years) and more likely to have hypertension and prior diagnosed HF. African Americans had less prior diagnosed coronary disease, revascularization, hypothyroidism, or valve replacement. Atrial fibrillation was much less prevalent in African Americans (19.7%) than Caucasians (38.3).
Dang et al [8]	Atrial Fibrillation in a Multiethnic Inpatient Population of a Large Public Hospital	**2004**	**737**	**(16.4)**	**(11.1)**	**(59.2)**	**(10.3)**	--	Compared to Caucasians, left ventricular hypertrophy was more common in African-American and Asians. At discharge, Caucasians more frequently had coronary artery disease compared to Hispanics, African Americans, and Asians; cardiomyopathy was less common in Caucasians as compared to African Americans, Hispanics and Asians.

Bush et al [9]	Atrial Fibrillation among African Americans, Hispanics and Caucasians: Clinical Features and Outcomes from the AFFIRM Trial	**2006**	**4060**	**3,599 (90.1)**	**--**	**132 (3.3%)**	**265 (6.6)**	**--**	African Americans were more likely female and hypertensive and Hispanics had higher prevalence of cardiomyopathy. Survival was better for rate control than rhythm control in Caucasians, equivalent in African Americans and better for rhythm control in Hispanics.
Novaro et al [10]	Meta-analysis comparing reported frequency of atrial fibrillation after acute coronary syndromes in Asians versus whites	**2008**	**(94,785)[x]**	**(93,050)**	**(1,735)**	**--**	**--**	**--**	Asians experiencing acute ischemic syndromes have a significantly lower frequency of AF compared with whites
Borzecki et al [11]	Racial differences in the prevalence of atrial fibrillation among males	**2008**	**(5.3% Of 664,754)**					**--**	White males have the highest AF burden even after adjustment for known risk factors. Of predisposing conditions, whites were more likely to have valvular heart disease, coronary artery disease and congestive heart failure, blacks had the highest hypertension prevalence; Hispanics had the highest diabetes prevalence.
Shen et al [12]	Racial/Ethnic Differences in the Prevalence of Atrial Fibrillation Among Older Adults—A Cross-Sectional Study	**2010**	**22807 [5.3% of 430 317]**	**(8.0)**	**(3.9)**	**(3.6)**	**(3.8)**	**--**	Atrial fibrillation is less prevalent in older nonwhite individuals than whites. White race/ethnicity is associated with significantly greater odds for atrial fibrillation compared to blacks, Asians, and Hispanics, after adjusting for comorbidities.
Meschia et al [13]	Racial disparities in awareness and treatment of atrial fibrillation: The REasons for Geographic and Racial Differences in Stroke (REGARDS) study	**2010**	**432**	**344**	**--**	**--**	**88**	**--**	Blacks were less likely than whites to be aware of having atrial fibrillation or to be treated with warfarin
Sun et al [4]	Comparison of frequency of atrial fibrillation after coronary artery bypass grafting in African Americans versus European Americans	**2011**	**2342**	**1,838**	**--**	**--**	**504**	**-**	AF was significantly less common among African-American patients than among European-American patients after coronary artery bypass grafting
Current study	Prevalence, Trends and Outcome of Middle-eastern Arab and South Asian Patients Hospitalized with Atrial Fibrillation	**--**	**3405**	**--**	**548**	**--**	**--**	**2857**	Arabs hospitalized with AF were older in age and had higher prevalence of co-morbid cardiovascular risk factors compared to Asians. Arabs had higher in-hospital mortality rate whereas the stroke rate was comparable

4.1.9.2. Table2. Atrial fibrillation patients' demographics, clinical characteristics and outcomes according to Arab and Asian

Variable	Arab (N=2857)	Asian (N=548)	P value
Other Cardiac (%)			
Acute coronary syndrome	6.9	9.9	0.02
Heart failure	20	12.4	0.001
Valvular heart disease	3.7	6.8	0.001
Patient characteristics at admission (%)			
Age in year (mean ±SD)	58±16	49±11	0.001
Body mass index (kg/m2) (mean ±SD)	31±10	27±6	0.001
Cardiovascular risk factors (%)			
Current smoker	11.3	13.9	0.09
Hypertension*	41.7	28.8	0.001
Diabetes mellitus†	34.6	17.7	0.001
Chronic renal impairment	5.7	1.6	0.001
Dyslipidemia††	10.4	6.9	0.01
Prior cardiovascular disease (%)			
Prior myocardial infarction	11.9	9.5	0.11
Prior atrial fibrillation	85.4	86.1	0.64
Peak CK-MB (mean ±SD)	36±222	44±286	0.68
Left ventricular ejection fraction (%)			
Normal: LVEF of ≥ 55%	33.1	29.4	0.63
Mild: LVEF of 40%-54%	36.4	35.9	
Moderate: LVEF of 30%-39%	14.4	18.3	
Severe: LVEF of < 30%	16.1	16.3	
Hospital days (mean ±SD)			
CCU stay	2.5±2	2±1.5	0.004
Total hospital stay	4.4±4	3.9±3	0.01
In hospital outcome (%)			
Death	4.8	2.6	0.02
Stroke	0.5	0.4	0.70

Data are expressed in numbers (%) of patients unless otherwise indicated.
*Systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, or current antihypertensive treatment. †Patient had been informed of the diagnosis by a physician before admission and for type 1 or 2 diabetes.
†† Total cholesterol >5.2 mmol/L or current use of lipid-lowering agent.
‡Of patients eligible for thrombolysis (ST-elevation myocardial infarction (previously known Q wave MI) or new or presumed left bundle branch block). CABG = coronary artery bypass graft; CCU = coronary care unit; MI = myocardial infarction; STEMI = ST elevation myocardial infarction; NSTEMI = non ST elevation myocardial infarction

4.1.9.3. Table 3. Medication received before, during admission and at discharge in AF patients according to Arab and Asian

Medications	Before Admission			During Admission			At Discharge		
	Arab	Asian	P value	Arab	Asian	P value	Arab	Asian	P value
Aspirin	29.5	21.2	0.001	47.7	47.3	0.85	51.1	51.5	0.88
Warfarin	1.5	2.2	0.27	17.6	20.6	0.09	31.8	39.4	0.001
Clopidogrel	2.9	2.6	0.68	4.9	4.6	0.76	4.1	3.6	0.65
Beta blocker	9.2	11.1	0.16	20.8	29.9	0.001	14.8	24.1	0.001
CCB	4.6	3.5	0.26	11.2	6.6	0.001	13.7	8.2	0.001
Digoxin	48.9	43.6	0.02	48.9	43.6	0.02	41.3	35.8	0.02
ACE inhibitors/ARBs	10.4	8.8	0.24	27.9	26.3	0.43	31.6	28.5	0.15
GPIIb/IIIa inhibitors				0.3	0.9	0.04			
Unfractionated heparin				26.6	29.4	0.17			
LMWH (enoxaparin)	0.3	0	0.19	9.9	15.5	0.001	0.4	0.4	0.96
Antiarrhythmics	25.4	14.6	0.001	63.9	60.4	0.12	50.4	43.2	0.002

Data are expressed in numbers (%) of patients unless otherwise indicated.
GP = glycoprotein; LMWH = low molecular weight heparin; CCB = calcium channel blockers;
ACE=angiotensin converting enzyme inhibitor, ARB=angiotensin receptor blocker.

4.1.9.4. Table 4: Trend of outcomes (1990 to 2010), including mortality and stroke in AF patients according to Arab and Asian

Outcomes	1991-94	1995-98	1999-02	2003-06	2007-10	P value
Number	595	808	425	778	799	
Age (mean±SD),yrs	55.7±16	56±15	56±16	56±16	58±16,	0.046
Arab (%)	18.1	24.8	12.7	22.3	22.1	0.001
Mortality rates (%)	4.4	4.1	5.4	4.9	4.0	0.76
Arab	4.8	4.2	5.8	5	4.8	
Asian	1.3	3	3.2	4.3	1.2	
P value	0.15	0.57	0.41	0.70	0.04	
Stroke rates (%)	0.3	0	0.2	0.4	1.3	0.69
Arab	0.2	--	0.3	0.5	1.4	
Asian	1.3	--	0	0	0.6	
P value	0.12	--	0.68	0.41	0.39	
Diabetes Mellitus (%)	27.2	30	31.5	35.7	33.8	0.001

Arab	28.8	32.4	34.2	39.2	37.1	
Asian	16.7	12.1	16.1	18.4	21.4	
P value	0.03	0.001	0.005	0.001	0.001	
HTN (%)	29.4	32.1	40	46.9	47.6	0.001
Arab	30.9	32.7	42.7	50.4	51.2	
Asian	19.2	27.3	24.2	31.2	33.9	
P value	0.03	0.28	0.006	0.001	0.001	
ACS (%)	3.4	4.1	8.2	7.5	13.1	
Arab	3.1	3.5	7.7	7.7	12.5	
Asian	5.1	8.1	11.3	6.4	15.5	
P value	0.35	0.03	0.34	0.59	0.31	
Valvular HD (%)	2.9	6.3	4.5	3.1	4.1	0.001
Arab	2.7	6.1	3.9	2.7	3.0	
Asian	3.8	8.1	8.1	5	8.3	
P value	0.57	0.44	0.14	0.15	0.002	
RHD (%)	5.2	2.7	2.1	0.1	1.5	0.001
Arab	4.6	2.4	1.1	0.2	1.4	
Asian	9	5.1	8.1	0	1.8	
P value	0.11	0.13	0.001	0.64	0.73	
Warfarin (%)	17	32.3	31.3	35.6	44.1	0.001
Arab	15.9	31.2	30.9	36.1	41.7	
Asian	24.4	40.4	33.9	33.3	53.0	
P value	0.06	0.07	0.64	0.53	0.009	

Data are expressed in numbers (%) of patients. HTN= hypertension, ACS= acute coronary syndromes, Valvular HD= valvular heart disease, RHD= rheumatic heart disease

4.1.9.5. Table 5. Multivariate analysis of predictors of in-hospital mortality in AF patients.

Variable	Adjusted OR	95% C.I.	P value
Patients' characteristics			
Arab	1.30	0.71 – 2.47	0.38
Age	1.04	0.03 – 1.05	0.001
Diabetes mellitus	1.50	1.04 – 2.15	0.03
Hypertension	0.81	0.56 – 1.17	0.26
Chronic renal impairment	2.20	1.31 – 3.73	0.003
Cardiogenic Shock	96	25 – 362	0.001

OR= odd ratio; C.I.= confident interval, LV= left ventricular.

4.1.10. Figures

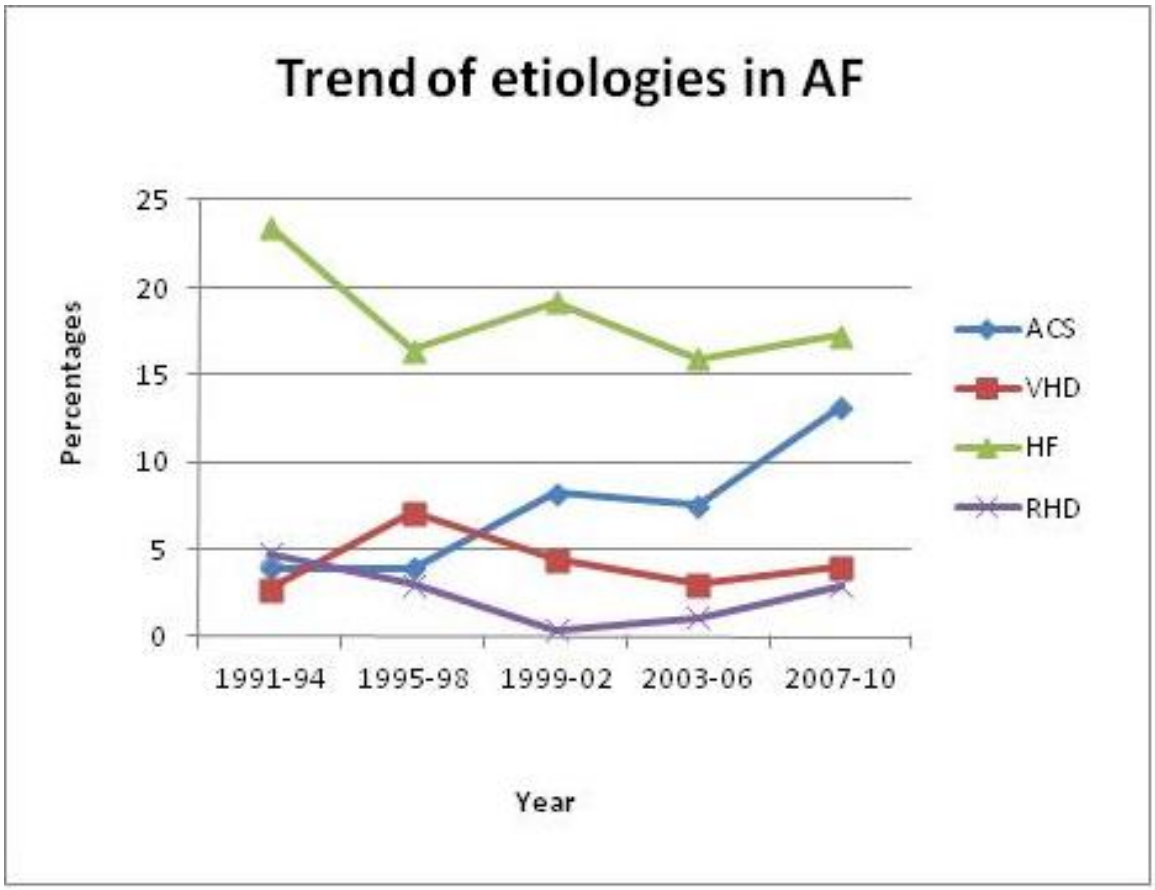

Figure 3 Secular Trends of AF aetiologies & co-morbidities over 20 years

4.2. Women hospitalized with atrial fibrillation: gender differences, trends and outcome from a 20-year registry in a Middle Eastern country (1991-2010)

4.2.1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice accounting for approximately one-third of hospitalizations for cardiac rhythm disturbances [1,2]. While there are an increasing number of studies addressing the issue of gender differences in other cardiovascular diseases particularly coronary artery disease [3-4], nonetheless, only few studies have dealt with gender differences and AF [5-14].

Some studies suggested less favorable outcomes with higher relative mortality, a higher risk of stroke and an underuse of anticoagulants in women [15-19]. However, results from these studies were not consistent and included relatively small numbers of women over a short time period. Moreover, to date most of the previously published studies were limited by the fact that they were conducted in the developed world and included mainly Caucasian patients. Data about women with atrial fibrillation among other ethnicities are very limited. Data on nonblack minorities are even scarcer. The current study extends these observations in unique ethnicities that have not been adequately studied previously; (Middle Eastern Arabs and South Asians) and reports for the first-time secular trends of patients hospitalized with AF according to gender over a 20-years period.

4.2.2. Materials and methods

Study setting, definitions and statistical analysis are the same as described in section 4.1.2. [20-26].

4.2.3. Results

Overall, from the year 1991 to end of 2010, a total of 41,438 patients with acute cardiac disease were hospitalized. 3849 of patients were admitted with AF and 37589 patients were admitted with other cardiovascular diagnoses and no-AF. Among AF patients; 1417 (36.8%) were women and 2432 (63.2%) were men.

4.2.3.1. Baseline clinical characteristics (Table 1)

Women were 5 years older and more likely to have hypertension, diabetes mellitus, dyslipidemia and chronic renal impairment, but less likely to be current smokers, have prior history of myocardial infarction or heart failure when compared to men. Rheumatic heart disease was more common among women than men. Body mass index was less in men (29±9 versus 32±10, p = 0.001). Sub-analysis according to ethnicity revealed that South Asian women were significantly younger than their Middle Eastern Arab counterparts (53 ±14 vs. 60 ±15 years, p=0.001). Preserved left ventricular function was more common among women when compared to men, while the length of stay was significantly longer among women when compared to men.

4.2.3.2. Medications (Table 2)

Prior to admission: At the time of admission; women were more likely to be on aspirin, digoxin, antiarrhythmics, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACE/ARB) and calcium channel blockers when compared to men. beta-blockers, warfarin and clopidogrel use were comparable between the two groups.

Admission: Women were more likely to be treated with beta-blockers and calcium channel blockers and less likely to be treated with enoxaparin. There was no gender preference in the

use of anticoagulation with Warfarin. Antiplatelets, ACE/ARB, antiarrhythmics and unfractionated heparin use were comparable between the two groups.

Discharge: Women were more likely prescribed calcium channel blockers, antiarrhythmics and digoxin than men whereas warfarin and antiplatelets were comparable between the two groups.

4.2.3.3. Outcomes and trends (Table 3)

In-hospital mortality and stroke rates were found comparable in relation to gender. Over the 20-year period, patients hospitalized with AF in the latter period were 2 years older and more likely to be female when compared to those hospitalized in the 1990s. Moreover, in the latter years, there was increase in the prevalence of diabetes mellitus and hypertension in both groups but more so in women when compared to patients hospitalized in the earlier years.

Associated ischemic heart disease was also trending higher in both groups while valvular heart disease and heart failure prevalence was trending lower with no significant difference between the two groups. Rheumatic heart disease was statistically trending lower in prevalence but more prevalent in women. There were no significant differences in mortality or stroke rates over the study period between the two groups.

The use of warfarin was significantly trending higher over the study period but no differences were found between men and women.

4.2.3.4. Predictors of in-hospital mortality (Table 4)

Multivariate predictors of poor outcome among patients hospitalized with AF are age, diabetes mellitus, chronic renal impairment and cardiogenic shock. Gender was not an independent predictor of poor outcome.

4.2.4. Discussion

The current study demonstrates for the first time 20-years observations of the clinical characteristics, treatment and outcome of patients hospitalized with AF according to gender. Consistent with reports from the developed world, women were older and more likely to have cardiovascular risk factors including diabetes mellitus, hypertension and chronic renal impairment. Rheumatic heart disease was more common among women, while prior history of myocardial infarction was more common among men. The survival of patients hospitalized for atrial fibrillation was comparable between both genders. Overall the 20-years study period, there were significant variations in the prevalence of concomitant acute cardiac diseases among women hospitalized with AF with an increase in ischemic heart disease and decrease in the prevalence of valvular heart disease and heart failure in the latter years of the study.

4.2.4.1. Baseline Characteristics

The prevalence and clinical characteristics of women hospitalized for atrial fibrillation has been described by many investigators [5-13] (Table 5). Almost exclusively, women presenting with atrial fibrillation were older than men as was observed in the current study. Interestingly, the mean age of Asian women (53 years) hospitalized with AF in the current study is much younger than any previous reports of women hospitalized with AF (59-77.5 years) [5-14].

Our study also demonstrated a higher prevalence of co-morbidities in women; women were more likely to have hypertension, diabetes mellitus, dyslipidemia, chronic renal impairment, obesity and rheumatic heart disease. This is also consistent with previous reports. The Canadian Registry of AF (CARAF) [27] investigators demonstrated that, at the time of initial presentation of atrial fibrillation, men have a higher burden of ischemic heart disease whereas women have a higher prevalence of hypertension and a history of thyroid dysfunction. The Framingham study [28] cohort suggested that there were higher incidences of congestive heart

failure, valvular heart disease, and diabetes in women. In addition the Euro Heart Survey on Atrial Fibrillation [9] showed that women with AF had more co morbidities, more heart failure with preserved systolic function than men. Consistent with these reports diabetes mellitus and hypertension are more common among women than men in our study. Furthermore, the prevalence of diabetes mellitus is much higher than any previous reports. This is consistent with the high prevalence of diabetes mellitus in the Arab Middle east in general and in Qatar specifically and may in part explain the relatively younger age of AF female patients among both Asian and Middle Eastern Arabs. We have recently reported very high prevalence of diabetes mellitus among patients presenting with acute coronary syndrome [22], and among patients presenting with heart failure [21].

4.2.4.2. Treatment

The most important goal in atrial fibrillation treatment is obviously to reduce the risk of stroke with anticoagulation [29]. We report equal use of anticoagulants and antiplatelets among both sexes in our patients. This is in contrast to some reports that suggested that women were less likely to receive warfarin than their male counterparts [19]. According to the CARAF [27], women 75 years of age and older were 54% less likely to receive warfarin, compared with men in this age group. Additionally, results from a British community survey of warfarin use in patients with atrial fibrillation, the lowest warfarin use was among elderly women [30].

Our study also highlights the suboptimal use of oral anticoagulation in patients with atrial fibrillation in spite of convincing evidence from large randomized trials showing that anticoagulation significantly reduces stroke rates in patients with AF [31]. Our findings are consistent with results of studies conducted during the same period; Majeed and colleagues study in general practice in England and Wales, reported the rate of warfarin use was low; 20% to 34% in men and 17% to 25% in women between 1994 and 1998 [32]. Our results are also

concordant with the 23% found by Sudlow and colleagues in an earlier study from the north of England [30] and the 31% reported by Kalra and associates [33]. A higher treatment rate of 55% was reported by Go and colleagues in northern California during that period, however [34]. More recently the Euro Heart Survey on Atrial Fibrillation, reported higher prescription rate of oral anticoagulants (65%) which was identical in both genders [9].

Although the rate of patients who had contraindications to anticoagulation is unknown in the current study, previous investigators estimated that between 40–60% of patients might benefit from anticoagulation [30, 35]. Nonetheless, our results are encouraging in that there was significant increase in the use of anticoagulants over the 20 years period from 18.7 % to 44.7%.

4.2.4.3. Outcomes and trends

Evidence from the Framingham study [20] suggests that there is no sex difference in mortality rate in patients with atrial fibrillation. Our study further supports this by the finding of lack of gender difference in in-hospital mortality rates. In contrast, in the United States, in-hospital mortality rate following admission for atrial fibrillation is estimated at 0.8%. Men have a modestly higher (but statistically significant) risk of in-hospital mortality [36]. Using administrative data (National Hospital Discharge Survey), Kairallah and colleagues [37] demonstrated that male sex was an independent predictor of in-hospital mortality. However, analysis of administrative data from Scotland suggests that 1-year mortality may be higher in women; Stewart and colleagues [38] found the 1-year case fatality rate in men to be 11.9% v. 16.2% in women. The distribution of ages in this cohort is not known; it was argued that the higher mortality rate seen in women may reflect a greater number of very elderly women diagnosed with atrial fibrillation. In addition, Wattigney and colleagues [39] have demonstrated in a US cohort that mortality remains higher among men after age standardization.

In our study there was no gender difference in in-hospital stroke rates. Previous investigations on stroke outcomes in men and women provided contradictory results. The higher stroke rate among women observed in the Framingham study [40], led to the incorporation of female gender in the Framingham stroke risk scheme [41]. Moreover, results of the SPAF (Stroke Prevention in Atrial Fibrillation) trials [42] and the ATRIA (AnTicoagulation and Risk factors In Atrial fibrillation) study, showed a higher risk for AF-related thromboembolism in women not receiving oral anticoagulation [7]. Similarly, in the Euro Heart Survey on Atrial Fibrillation [9] women had a higher rate for stroke than men, mainly when withholding oral anticoagulation from women undergoing rhythm control and having at least 1 stroke risk factor. But no further differences were found regarding 1-year outcomes. The reason why our study did not show any gender difference in stroke incidence is probably because we only studied in-hospital short term outcomes. In addition, the absolute number of stroke events is too small to derive any statistical power of significance (table 1). Further long-term stroke outcome AF studies from our region are eagerly awaited to further clarify this issue.

One exciting part of our study is the trends of etiologies of atrial fibrillation over the 20-year period of study. The increased trend of associated ischemic heart disease and hypertension was accompanied by a reduced trend in rheumatic heart disease and heart failure while valvular heart disease was constant. An earlier report in 2000 by Miyasaka and colleagues reported Secular Trends in Incidence of Atrial Fibrillation in Olmsted County, Minnesota, from 1980 to 2000, focused on AF incidence and prevalence projections in the USA [43]. More recently, Piccini and colleagues [2] examined trends in the incidence and prevalence of AF and associated mortality among Medicare beneficiaries with incident AF between 1993 and 2007. Apart from these two reports to the best of our knowledge the medical literature is devoid from studies addressing secular trends in the incidence and subsequent mortality in a contemporary,

nationally representative sample of patients similar to our study. More so, long-term gender trend studies in AF are basically non-existent.

Moreover, given the improvements in the recognition and management of the co-morbid conditions associated with AF, especially hypertension, heart failure, and coronary artery disease, one would expect an improvement in the clinical outcome and prognosis. This was not the case as demonstrated by the steady rate of mortality over the 20 years of our study. Although our analysis was limited to in hospital outcomes, nonetheless our findings are consistent with the study by Miyasaka and colleagues [43,44] addressing longer term mortality. They reported that mortality risk was high, especially within the first 4 months, but more importantly; there was no evidence for any significant changes over the 21 years in terms of overall mortality, early or late mortality, or mortality among patients without preexisting cardiovascular disease.

Further studies are urgently needed addressing the trends in cardiovascular profiles and therapeutic interventions in both sexes and how they affect outcome in terms of morbidity and mortality in order to develop gender-specific tailored strategies for the prevention of cardiovascular disease around the world.

4.2.5. Conclusions

The results of this 20-years observational study in residents of a Middle-eastern country provide for the first time insights into the characteristics, treatment practices, and in-hospital outcome among Middle-eastern Arab and South Asians ethnicities. To the best of our knowledge the current study is the first ever report of gender trends in etiologies of AF over a 20-year period. The current study also underscores the urgent need to study gender differences in atrial fibrillation among various ethnicities.

4.2.6. References

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4.2.7. Tables

4.2.7.1. Table1. Atrial fibrillation patients' demographics, clinical characteristics and outcomes according to gender

Variable	Men (n=2432)	Women (n=1417)	P Value
Patient characteristics at admission			
Age in year (mean ±SD)	54.5±15.7	59±15	0.001
Body mass index (kg/m2) (mean ±SD)	29±9	32±10	0.001
Ethnicity			
Middle Eastern Arabs	67.3	86.1	
South Asians	19	6.1	
Others	13.7	7.8	0.001
Age in different ethnicities (years) (mean ±SD)			
Middle Eastern Arabs age	56.6±17	60±15	0.001
South Asians	49±11	53±14	0.001
Others	52±13	54±14	0.001
Concomitant cardiac diagnoses			
Acute coronary syndrome	7.9	6.9	0.30
Heart failure	17.6	18.8	0.38
Valvular heart disease	3.3	6.1	0.001
Cardiovascular risk factors			
Current smoker	18.9	1.3	0.001
Hypertension*	32.1	49.5	0.001
Diabetes mellitus†	25.7	37.5	0.001
Chronic renal impairment	4	6	0.005
Dyslipidemia††	7.9	12.3	0.001
Prior myocardial infarction	12.3	8.3	0.001
In-hospital therapy			
Rate of thrombolysis‡	1.8	0.8	0.01
Percutaneous coronary intervention	0.4	0.4	0.78
Left ventricular ejection fraction			
Normal: LVEF of ≥ 55%	27.2	41.2	0.001
Mild: LVEF of 40%-54%	34.9	38.2	0.001
Moderate: LVEF of 30%-39%	16.5	12	0.001
Severe: LVEF of < 30%	21	8.6	0.001
Hospital days (mean ±SD)			
CCU stay	2.4±2	2.6±2	0.06
Total hospital stay	4±4	4.7±4	0.001
In hospital outcome			
Death	97(4)	63(4.4)	0.49
Stroke	9(0.4)	6(0.4)	0.80

Data are expressed in percent % of patients unless otherwise indicated, CCU = coronary care unit, SD= standard deviation

*Systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, or current antihypertensive treatment. †Patient had been informed of the diagnosis by a physician before admission and for type 1 or 2 diabetes.

†† Total cholesterol >5.2 mmol/L or current use of lipid-lowering agent.

‡Of patients eligible for thrombolysis (ST-elevation myocardial infarction (previously known Q wave MI) or new or presumed left bundle branch block)

4.2.7.2. Table 2. Medication received before, during admission and at discharge in AF patients according to gender

Medications	Before Admission			During Admission			At Discharge		
	Men	Women	P value	Men	Women	P value	Men	Women	P value
Aspirin	25	31.2	0.001	47.7	46.4	0.44	51.4	50.3	0.52
Warfarin	1.6	1.8	0.59	18.1	18.8	0.56	33.8	35.6	0.24
Clopidogrel	2.5	2.9	0.52	5.2	4.6	0.41	4.5	3.3	0.08
Beta blocker	9.4	10.1	0.47	25.4	19.5	0.001	18.1	15.4	0.03
CCB	2.8	6.7	0.001	8.3	13	0.001	10	15.9	0.001
Digoxin	16.7	26.9	0.001	46.2	49.1	0.08	36.2	45.7	0.001
ACE inhibitors/ARBs	9.1	11.6	0.02	26.6	27.4	0.60	29.7	32.3	0.10
GPIIb/IIIa inhibitors				0.5	0.2	0.13			
Unfractionated heparin				28.2	25.9	0.12			
LMWH (enoxaparin)	0.2	0.4	0.22	12.7	9.5	0.003	0.4	0.4	0.96
Antiarrhythmics	18.6	29.3	0.001	62.6	63.2	0.72	45.1	54.1	0.001

Data are expressed in percent % of patients unless otherwise stated.
GP = glycoprotein; LMWH = low molecular weight heparin; CCB = calcium channel blockers; ACE=angiotensin converting enzyme inhibitor, ARB=angiotensin receptor blocker.

4.2.7.3. Table 3: Secular trends of risk factors, warfarin use and outcomes (including mortality and stroke) in AF patients according to gender (1990 to 2010)

Outcomes	1991-94	1995-98	1999-02	2003-06	2007-10	P value
No.	648	900	474	891	935	
Age (mean±SD),yrs	55±16	56±15	56±15.6	56±16	57.5±16	0.02
Women No. (%)	215(33.2)	350(38.9)	181(38.2)	349(39.1)	322(34.4)	0.04
Mortality rates	4.5	3.7	5.1	4.5	3.6	0.63
Men	4.6	3.6	4.4	4.4	3.3	
Women	4.2	3.7	6.1	4.6	4.3	
P value	0.80	0.95	0.43	0.91	0.40	
Stroke rates	0.3	0	0.2	0.3	1.1	0.007

Men	0.5	0	0	0.2	1.1	
Women	0	0	0.6	0.6	0.9	
P value	0.32	--	0.20	0.33	0.77	
Diabetes Mellitus	25.6	27.4	30.8	32.9	32.5	0.004
Men	24.9	23.6	25.6	26.5	27.4	
Women	27	33.4	39.2	42.7	42.2	
P value	0.58	0.001	0.002	0.001	0.001	
HTN	28.7	30.7	40.3	45.1	45.7	0.001
Men	23.1	24.9	33.4	38.3	38.8	
Women	40	39.7	51.4	55.9	58.7	
P value	0.001	0.001	0.001	0.001	0.001	
ACS	3.9	3.9	8.2	7.5	13.2	0.001
Men	4.2	4	10.2	7.9	12.7	
Women	3.3	3.7	5	6.9	14	
P value	0.58	0.83	0.04	0.56	0.59	
Valvular HD	2.7	7.1	4.4	3.0	4	0.001
Men	1.6	4.4	4.1	2.6	3.8	
Women	4.7	11.4	5.0	3.7	4.3	
P value	0.02	0.001	0.65	0.33	0.66	
Heart Failure	23.5	16.4	19.2	15.9	17.3	0.001
Men	23.6	14.5	19.5	16.2	16.6	
Women	23.3	19.4	18.8	15.5	18.6	
P value	0.93	0.05	0.86	0.77	0.44	
RHD	3.4	3	0.4	1.1	2.9	0.001
Men	4.2	1.1	0.7	0.7	1.6	
Women	6.0	6	0	1.7	5.3	
P value	0.29	0.001	0.26	0.17	0.002	
Warfarin	18.7	33.4	31.2	38.0	44.7	0.001
Men	18.2	32	33	37.6	43.2	
Women	19.5	35.7	28.2	38.4	47.5	
P value	0.69	0.25	0.26	0.80	0.21	

Data are expressed in percent % of patients unless otherwise stated. HTN= hypertension, ACS= acute coronary syndromes, Valvular HD= valvular heart disease, RHD= rheumatic heart disease

4.2.7.4. Table 4. Multivariate analysis of predictors of in-hospital mortality in AF patients

Variable	Adjusted OR	95% C.I.	P value
Patients characteristics			
Gender male	1.12	0.77 – 1.65	0.55
Age	1.04	1.02 – 1.05	0.001
Diabetes mellitus	1.52	1.03 – 2.26	0.04
Hypertension	0.86	0.58 – 1.29	0.46
Chronic renal impairment	2.09	1.18 – 3.68	0.001
Cardiogenic Shock	285	84 - 970	0.001

OR= odd ratio; C.I.= confident interval.

4.2.7.5. Table 5. Studies addressing gender differences in atrial fibrillation.

Table 8 Studies addressing gender differences in atrial fibrillation

Author	Study	Year conducted (or published)	Patients enrolled	Females with AF (%)	Mean age	Mean Follow-up	Conclusions
Friberg et al [5]	Comparison of the impact of atrial fibrillation on the risk of stroke and cardiovascular death in women versus men	3 cohort (1976-1978, 1981- 1983, and 1991-1994)	276	110 (40)	68	4.7 years	AF is a much more pronounced risk factor for stroke and cardiovascular death in women than in men
Wändell et al [6]	Five-year mortality in men and women with atrial fibrillation	1993 (2001)	129	53	77.5	5 years	AF is related to an excess sex- and age-standardized, 5-year mortality in women but not in men, with levothyroxine treatment as one significant factor
Fang et al [7]	Gender differences in the risk of ischemic stroke and peripheral embolism in atrial fibrillation: ATRIA study	1996-1997	13,559	5795 (43)		2.4 years	Women are at higher risk for AF-related thromboembolism off warfarin. Female sex is an independent risk factor for thromboembolism.
Essebag et al [8]	Sex differences in the relationship between amiodarone use and the need for permanent pacing in patients with atrial fibrillation	1997-	973	390 (40)	69.4	30 months	The risk of brady-arrhythmia requiring pacemaker insertion associated with amiodarone use for AF is significantly greater in women than in men, independent of weight or body mass index
Dagres et al [9]	Gender-related differences in presentation, treatment, and outcome of patients with atrial fibrillation in Europe: a report from the Euro Heart Survey on Atrial Fibrillation	2003-2004	5,333	2,249 (42)	70	One year	Women with AF had more co morbidities, more HF with preserved systolic function, and a lower QoL than men. Long-term QoL changes and other morbidities and mortality were similar.
Rienstra et al [10]	Gender-related differences in rhythm control treatment in persistent atrial fibrillation: data of the RACE study.	(2005)	522	192 (37)	71	2.3 years	In female patients with persistent AF, a rhythm control approach leads to more cardiovascular morbidity and mortality
Patel et al [11]	Outcomes and complications of	2005-2008	3265	518 (15.8)	59	Procedural	Females had lower procedural success rates and

	catheter ablation for atrial fibrillation in females						higher risk of bleeding complications than males
Roquer J. et al [12]	Comparison of the impact of atrial fibrillation on the risk of early death after stroke in women versus men	(2006)	1678	826 (49.8)	72.8	In-hospital	Adjusted for confounders, mortality is higher in men than in women although more women than men died during hospitalization, and AF is an independent poor predictor just for women
Forleo et al [13]	Gender-related differences in catheter ablation of atrial fibrillation	(2007)	221	71 (32)	61.6	22.5 months	Women are referred for AF ablation later with a more complex clinical pre-operative presentation. Despite this higher risk profile in women, no differences were detected in clinical outcomes
Current Study	Women Hospitalized with Atrial Fibrillation: Gender Differences, Trends and Outcome from a 20-year Registry in a Middle Eastern Country (1991-2010)	1991-2010	3849	1417	59	In-hospital	Women were 5 years older and had higher prevalence of co-morbid cardiovascular risk factors compared to men whereas, mortality and stroke rates were comparable. There was no gender preference in the use of anticoagulation.

AF= atrial fibrillation, ATRIA= (Anticoagulation and Risk Factors in Atrial Fibrillation) Study, QoL= quality of life, HF= heart failure, RACE= Rate Control versus Electrical cardioversion study.

4.3. Effect of age on treatment, trends and outcome of patients hospitalized with atrial fibrillation: insights from a 20-years registry in a Middle-Eastern country (1991-2010)

4.3.1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice accounting for approximately one-third of hospitalizations for cardiac rhythm disturbances [1,2]. It has long been established that AF is a disease of aging with AF incidence doubling with each decade of life [3]. Studies have estimated that the annual incidence of AF per 1000 person-years to be 1.9 in women and 3.1 in men younger than 65 years, but exceeds 32 per 1000 person-years in patients 80 years and older. Age-related declines in vascular compliance, increased population longevity, and the increasing prevalence of cardiovascular disease in older persons has led to an expanding AF epidemic in the developed world [2]. To date, most studies on AF epidemiology, treatment, and outcomes have been performed in North America and Europe involving mainly Caucasians patients [2-5] and while there are recognized ethnic differences in cardiovascular risk profiles [6], the world literature on epidemiology of AF in different ethnicities is limited [7], particularly concerning elderly patients.

Herein we studied the presentation, treatment and outcome of elderly patients aged above 70 years that were hospitalized with AF in a Middle-eastern country over a 20-year period and compared them to younger age groups.

4.3.2. Materials and methods

Study setting, definitions and statistical analysis are the same as described in section 4.1.2. [8,9].

4.3.3. Results

Between the year 1991 to end of 2010, a total 3848 consecutive patients were admitted with AF. 1345 patients were ≤50 years, 1759 were between >50 and 70 years and 744 patients were >70 years old.

4.3.3.1. Baseline clinical characteristics (Table 1)

A higher percentage of women was observed in the older age patients (groups 2 & 3 vs. 1). The older the AF patient the more likely to have hypertension and chronic renal impairment. Current smoking was more prevalent among the younger age group. The incidence of concomitant diagnosis of acute coronary syndrome, prevalence of prior myocardial infarction, prior coronary artery grafting and aortic stenosis were higher among the older age groups, while rheumatic heart disease and prior diagnosis with atrial fibrillation were more prevalent among the younger age group. The left ventricular ejection fraction was lower in the older age groups.

4.3.3.2. Medications (Table 1 & 2)

At the time of admission, the older age groups were more likely on beta-blockers, calcium-channel blockers, diuretics, ACE/ARB, antiplatelet agents, hydralazine, nitrates, digoxin and antiarrhythmics when compared to the younger age group.

Admission: The older age groups were more likely treated with beta-blockers, calcium channel blockers, diuretics, ACE/ARB, hydralazine and inotropes, while the younger age groups were more likely to be treated with antiarrhythmics.

Discharge: Older age groups were more likely prescribed calcium-channel blockers, diuretics, ACE/ARB, antiplatelet agents, hydralazine, digoxin and antiarrhythmics. Patients above 70 years were significantly less likely to be prescribed warfarin at time of discharge compared to the other two age groups.

4.3.3.3. Outcome (Table 1)

Older age AF patients had significantly higher in-hospital mortality and stroke rates when compared to the younger age groups.

4.3.3.4. Trend of Hospitalization and Outcome (Table 3)

Over the 20-year period, the total number of patients hospitalized with AF increased accompanied by an increase in the mean age from 54.9 to 57.5 years. The in-hospital mortality rate for the overall group was stationary ranging between 5.1% and 3.6%. It was however significantly lower in the younger age groups compared to higher age groups all through the study duration.

Secular trends analysis showed that the associated acute coronary syndromes, hypertension and diabetes mellitus prevalence were trending higher in the elderly group while heart failure prevalence was trending lower. There were no significant differences in mortality trends in the elderly group while stroke rate was higher. The use of warfarin as well as aspirin in the elderly group was significantly trending higher over the study period.

4.3.3.5. Multiple logistics regression analysis (Table 4)

Acute coronary syndrome presentation was associated with increased risk of death. Whereas ACE/ARBs and beta-blockers administration at admission was associated with reduced risk of death. Age alone was not predictor of in-hospital mortality.

4.3.4. Discussion

The current study using a large data of unselected consecutive AF patients admitted over 20-years in a Middle-Eastern country demonstrates important differences between older and

younger patients in the clinical profile, management, and prognosis. Elderly patients were more likely to have hypertension and chronic renal impairment. There was also a higher prevalence of associated coronary artery disease and aortic stenosis in elderly patients with a lower left ventricular ejection fraction than the younger age groups. Consistent with previous reports, we report a lower use of anticoagulation in the elderly group but there was no underuse of other evidence-based medications such as ACE/ARBs and beta-blockers when compared to younger patients contrary to most other published reports. The use of warfarin as well as aspirin in the elderly group was significantly trending higher over the study period. The older age AF patients had significantly higher in-hospital mortality and stroke rates with no significant changes in mortality trends over the 20-years of study. A higher trend of the associated acute coronary syndromes, hypertension and diabetes mellitus prevalence was observed in the elderly group. The current study underscores the urgent need to study elderly AF patients among various ethnicities.

4.3.4.1. Baseline Characteristics

The prevalence of diabetes mellitus in the current study is higher than that reported in any AF trial or registry regardless of age. This is consistent with the high prevalence of diabetes mellitus in the Arab Middle-east in general and in Qatar specifically and may in part explain the relatively younger mean age of patients observed in the study. Moreover, the prevalence of diabetes mellitus among patients increased further in the latter years when compared to the earlier years of the study regardless of age. This increase reflects the worldwide epidemic of diabetes mellitus, which is expected to get worse by 2030 particularly in Asia [10].

Our study also showed an increased prevalence of acute coronary syndrome (ACS) as a concomitant diagnosis with AF significantly more in the elderly group and was associated with higher complication rate. This finding is consistent with previous studies that have shown that

new onset AF was associated with increased short- and long-term mortality in patients presenting with ACS [11]. Indeed ACS was a significant predictor of mortality in our multivariate analysis.

4.3.4.2. Treatment

Our study also demonstrated the under-utilization of oral anticoagulants (OAC) in patients with AF especially in the elderly group despite the overwhelming evidence supporting OAC for stroke prevention. This finding is consistent with reports from other parts of the world. For example, a prospective cohort study reported by Hylek et al [12] reported that only 51% of hospitalized elderly patients with AF were initiated on OAC. Additionally, Bungard et al reported the prescription of OAC to patients with AF without contraindications to be between 15.2 and 78.8% [13]. Furthermore, a cross-sectional analysis from the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study cohort reported this figure to be only 55% [14]. We have not studied the reasons behind under-utilization of OAC in our group but reported reasons include physicians` underestimation to risk of stroke, overestimation of the risk of haemorrhagic complications, the frailty of elderly people, cognitive impairment, poor compliance of monitoring and treatment, falls risk, associated co-morbidity and concomitant medications [15] which may, indeed, play a role in our observations.

In addition, aspirin and clopidogrel were on the other hand more prescribed to our elderly patients as an alternative to warfarin. Aspirin therapy has indeed been shown to decrease the risk of stroke in AF; however, aspirin is not as effective as warfarin in stroke prevention [16]. Thus, electing to use aspirin instead of warfarin assumes that aspirin therapy offers a lower risk of intracranial haemorrhage (ICH) than warfarin therapy, which is supposed to balances the lower efficacy for stroke prevention. However, among patients above 75 years of age in the

Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) trial [17], there was no difference in the rates of ICH between aspirin- and warfarin-treated groups with a goal INR of 2.0 to 3.0. On the other hand, the Stroke Prevention in Atrial Fibrillation II (SPAF II) trial [18] (goal INR of 4.5) and the Japanese Nonvalvular Atrial Fibrillation–Embolism Secondary Prevention trial [19] both found significantly higher rates of ICH among warfarin-treated patients than among those treated with aspirin. These mixed results do not necessarily support the decision to favour aspirin therapy over warfarin therapy when treating elderly patients with AF who are at high risk for haemorrhagic complications but provide a legitimate basis for more frequent monitoring and a search for alternative agents in this higher risk age group. Additionally, Pengo V el al [20] observed a low rate of stroke and major bleeding in elderly patients above 75 being managed in an anticoagulation clinic for primary stroke prevention with low-intensity anticoagulation (INR 1.5-2.0). Although this is an option to be considered for certain patients, however further studies are required before such lower than usually targeted INR (2-3) can be formally recommended.

Interestingly, our study showed lack of underutilization of evidence-based medication in the elderly group. In fact, there was a significantly more use of ACE/ARB, Diuretics, Calcium channel blockers, Digoxin and Antiarrhythmics both at admission and on discharge. This finding is contradictory to previous studies from other part of the world that reported older age to be significantly associated with suboptimal use of evidence-based medications when compared to younger age groups, even in carefully monitored patients without apparent contraindications [21-23]. This was not, however, translated in improved survival and stroke rates which was higher in our elderly group.

4.3.4.3. Outcomes and trends

It was noted in our study that in-hospital mortality was higher in the elderly group and that the mortality was stationary over the 20-year study period. This was rather surprising given the improvements in the recognition and management of the co-morbid conditions associated with AF, especially hypertension, heart failure, and coronary artery disease that occurred over the years. To investigate this further we looked into the secular trends of co-morbidities that could be responsible for that lack of survival improvement that was expected. Indeed we found a significantly increasing prevalence of diabetes, hypertension and acute coronary syndromes (ACS) among elderly patients over the 20-year study period. Further analysis confirmed that ACS was in independent predictor of in-hospital mortality which may explain at least in part our observation of the lack of mortality benefit.

Although we are limited to the analysis of in-hospital mortality, however our findings are not inconsistent with other reports that showed lack of improvement in mortality trends over longer periods of study in other parts of the world. For example, Miyasaka and colleagues [24] studied mortality trends in patients diagnosed with first atrial fibrillation residents of Olmsted County, Minnesota, USA, (years 1980 to 2000) and reported that mortality risk was high, especially within the first 4 months, but more importantly; there was no evidence for any significant changes over the 21 years in terms of overall mortality, early or late mortality, or mortality among patients without pre-existing cardiovascular disease.

4.3.5. Conclusions

The results of this 20-years observational study in residents of a Middle-eastern country provide for the first-time insights into the characteristics, treatment practices, and in-hospital outcome among elderly patients from Middle-eastern Arab and South Asians ethnicities. The

study demonstrated that anticoagulation remains underutilized in elderly patients with AF in our region despite proven efficacy and increasing trends of cardiovascular comorbidities. The current study underscores the urgent need for prospective studies to investigate warfarin contraindications, relative warfarin efficacy and bleeding risks in our region to help guide healthcare providers in warfarin prescribing in this frail patient population and consequently reduce the risk of AF-related disabling strokes and mortality.

4.3.6. References

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4.3.7. Tables

4.3.7.1. Table1. Atrial Fibrillation patients' characteristics and co-morbidities according age

Age	**≤50 Yrs**	**51-70Yrs**	**>70Yrs**	**P-Value**
No	1345(35)	1759(45.7)	744(19.3)	
Patient characteristics at admission				
Female gender %	28.6	39	46.5	0.001
Race %				
Middle-eastern Arabs	63	75.8	90.6	
South Asians	22.2	13	2.8	
Others	14.9	11.1	6.6	0.001
Cardiovascular risk factors %				
Hypertension	14.3	49.1	57.1	0.001
Diabetes mellitus	9.3	41.4	40.7	0.001
Current smoker	18.4	10.9	5.1	0.001
Chronic renal impairment	1.5	4.7	10.8	0.001
Dyslipidemia	5.3	12.4	10.1	0.001
Prior cardiovascular disease %				
Prior myocardial infarction	1.6	14	20.2	0.001
Prior coronary artery bypass grafting	0.6	5.2	7.1	0.001
Rheumatic heart disease	4.2	2.2	0.1	0.001
Other current cardiovascular diagnoses %				
Acute coronary syndrome	2.6	8.8	13.3	0.001
Aortic stenosis	1.6	2.3	3.6	0.01
Mitral regurgitation	5.1	6.1	6.7	0.30
Pulmonary Hypertension	1.2	1.1	2.3	0.06

Preadmission medications %				
Beta-blockers	5.1	11.9	12.4	0.001
Calcium channel blockers	1.2	5.2	7.8	0.001
Diuretics	15.1	36	47.4	0.001
ACE/ARB	2.5	13.4	15.9	0.001
Antiplatelet agents	10.2	35	43.5	0.001
Hydralazine	0.1	0.8	1.5	0.002
Nitrates	0.3	4.3	7.5	0.001
Digoxin	12.7	22.6	29.3	0.001
Antiarrhythmics	14.6	24.8	31.6	0.001
Left ventricular ejection fraction, mean (SD), %	49±11	43±14.5	41±14	0.001
In-hospital outcome				
Death	19(1.4)	82(4.7)	58(7.8)	0.001
Stroke	3(0.2)	5(0.3)	8(1.1)	0.008

Data are expressed in percentage of patients unless stated.
ACE=angiotensin converting enzyme inhibitor, ARB=angiotensin receptor blocker.

4.3.7.2. Table 2. Treatment on Admission and at Discharge according to Age

%	**≤50Yrs**	**51-70Yrs**	**>70Yrs**	**P-Value**
On Admission				
betablockers	22.4	25.5	19.5	0.001
Calcium channel blockers	4.8	12.3	14.1	0.001
Diuretics	17	39.1	53.8	0.001
ACE/ARB	11.7	33.8	38.3	0.001
Antiplatelet agents	69.7	75.6	75.3	0.001
Hydralazine	0.1	1.4	2.3	0.001
Inotropes	1.6	7.8	8.3	0.001
Antiarrhythmics	69.2	59.5	59	0.001
Digoxin	49.1	45	49.3	0.001
At Discharge				
Beta-blockers	15.8	18.1	16.9	0.24
Calcium channel blockers	5.1	15.5	17.1	0.001
Diuretics	18.1	42.3	56.5	0.001
ACE/ARB	14.1	37.8	43.5	0.001
Antiplatelet agents	39.3	57.4	61.6	0.001
Clopidogrel	1.2	4.6	7.9	0.001
Aspirin	38.6	56.6	60.2	0.001
Warfarin	32.8	39.3	26.1	0.001
Antiarrhythmics	39.9	52.2	55	0.001
Digoxin	32.2	42.9	46	0.001

Data are expressed in percentage of patients unless stated.
ACE=angiotensin converting enzyme inhibitor, ARB=angiotensin receptor blocker.

4.3.7.3. Table 3. Secular Trends of the total and elderly AF groups over the 20-Years study period

Years	1991-94	1995-98	1999-02	2003-06	2007-10	P-Value
Total Group Trends						
Total No	648(16.8)	900(23.4)	474(12.3)	891(23.1)	935(24.3)	
Age, mean (SD), yrs	54.9±16	55.7±15	56±15.6	56±16	57.5±16	0.02
Sex- Female	215(33.2)	350(38.9)	181(38.2)	349(39.1)	322(34.4)	0.04
Death	29(4.5)	33(3.7)	24(5.1)	40(4.5)	34(3.6)	0.64
≤50Yrs	4(1.6)	5(1.6)	3(1.8)	4(1.3)	3(1.0)	
51-70Yrs	18(6.1)	18(4.1)	11(5.2)	18(4.6)	17(4.0)	
>70Yrs	7(6.5)	10(6.9)	10(10.9)	17(9.4)	14(6.4)	
P value	0.02	0.01	0.006	0.001	0.005	
Elderly Group Trends						
Number >70Yrs	107	145	92	180	220	
Mean age years ±SD	78±6	77.5±5.8	77±6	78±6.8	77.8±8.7	0.86
Women (%)	44.9	38.6	40.2	51.1	51.4	0.07
Mortality rates (%)	6.5	6.9	10.9	9.4	6.4	0.57
Stroke rates (%)	0	0	0	0.6	3.2	0.01
Diabetes Mellitus (%)	32.7	32.4	37	46.7	46.8	0.009
HTN (%)	49.5	45.5	54.3	67.8	60.9	0.001
ACS (%)	8.4	6.9	9.8	14.4	20.5	0.001
Heart Failure (%)	40.2	32.4	39.1	30.6	23.2	0.009
Valvular HD(%)	0.9	3.4	5.4	0.6	0.5	0.09
RHD (%)	0	0	0	0.6	0.5	0.78
Warfarin (%)	3.7	20.7	22.8	28.9	39.5	0.001
Aspirin (%)	47.7	57.9	54.3	63.9	67.3	0.001

Data are expressed in (percentage) of patients unless stated. HTN= hypertension, ACS= acute coronary syndromes, Valvular HD= valvular heart disease, RHD= rheumatic heart disease

4.3.7.4. Table 4. Multivariate predictors of in-hospital mortality

Variable	Adjusted OR	95% CI	P-Value
Age	1.01	0.98 – 1.05	0.50
Male gender	1.11	0.44 – 2.84	0.82
Acute coronary syndrome	4.36	1.77 – 10.74	0.001
Diabetes mellitus	2.22	0.86 – 5.72	0.10
Hypertension	0.69	0.25 – 1.90	0.47
Dyslipidemia	1.90	0.66 – 5.48	0.23
Chronic renal impairment	2.99	0.98 – 9.15	0.054
Current Smoking	1.01	0.32 – 3.20	0.98
Prior myocardial infarction (MI)	1.68	0.62 – 4.54	0.98
EF < 35	1.96	0.79 – 4.89	0.31
ACE/ARB *	0.19	0.05 – 0.63	0.007
Beta-blockers *	0.36	0.15 – 0.87	0.02

Antiplatelet agents *	1.00	0.27 – 3.74	1.00
Antiarrhythmics *	0.36	0.11 – 1.15	0.08
Digoxin*	1.10	0.22 – 5.40	0.91

Variables forced into model are: age, ACS, ACS, diabetes mellitus, hypertension, dyslipidemia, chronic renal impairment, current smoking, prior MI, past rheumatic heart disease, normal left ventricular ejection fraction (EF), ACE/ARB (ACE=angiotensin converting enzyme inhibitor, ARB=angiotensin receptor blockers), Beta-blockers and antiplatelet agents.
* Administered on admission

4.3.8. Figures

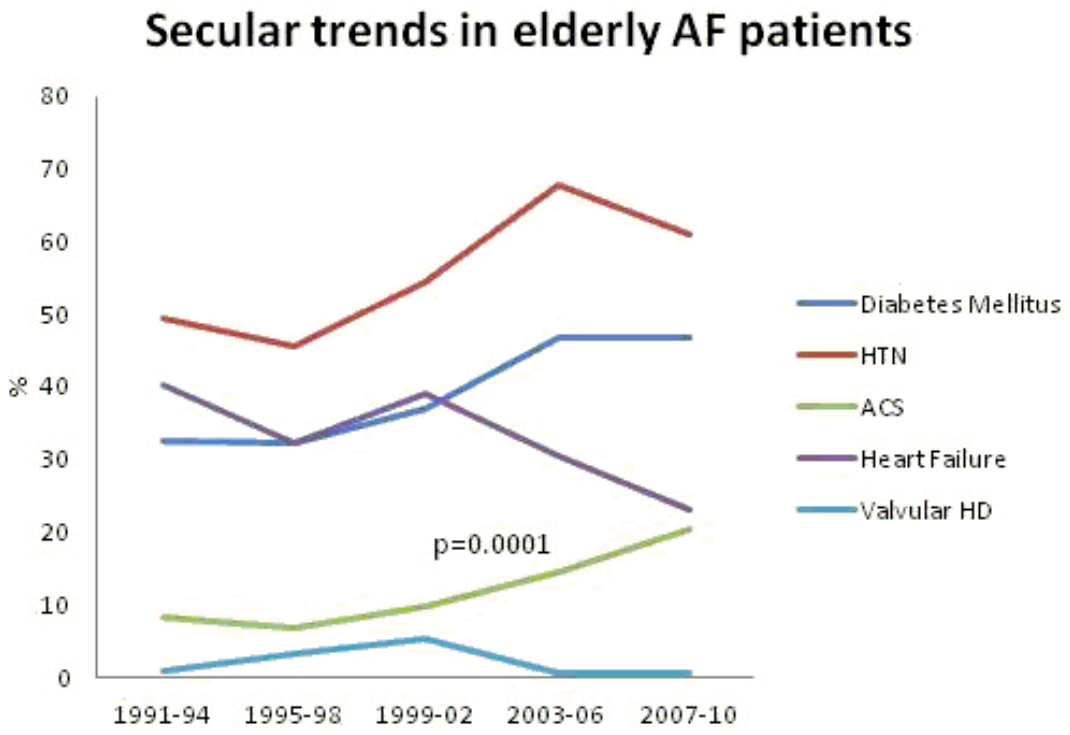

Figure 4 Secular Trends in elderly Patients

4.4. Atrial fibrillation in Middle Eastern Arab and South Asian patients hospitalized with acute myocardial infarction: experience from a 20-year registry in Qatar (1991-2010)

4.4.1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice accounting for approximately one-third of hospitalizations for cardiac rhythm disturbances [1]. AF has been reported to complicate the course of acute myocardial infarction (AMI) in about 6–21% of hospitalized patients [2]. There is increasing evidence that there are variations in the

susceptibility and incidence of AF complicating AMI in different ethnicities [3,4]. In addition, most of the available literature is derived from trials and studies performed in North America and Europe while other parts of the world are under-represented in AF research [5].

Herein, we study the incidence, predictors of AF after AMI and prognostic implications of this arrhythmia on in-hospital AMI outcomes in two ethnicities that have not been adequately studied together previously (Middle Eastern Arabs and South Asians), in a Middle Eastern country over a 20-years period.

4.4.2. Materials and methods

Study setting, definitions and statistical analysis are the same as described in section 4.1.2. [6-10].

4.4.3. Results

4.4.3.1. Patient Characteristics (Table 1)

Overall, from the year 1991 to end of 2010, a total of 12881 patients were hospitalized with acute myocardial infarction AMI. Of these 227 had AF during hospitalization (1.8%). There were 12.5% females in the overall AMI group; however females constituted 30% of patients who developed AF.

Patients with AF were significantly older than those without AF in all ethnicities especially Middle Eastern Arabs who had 10 year difference in mean age. Patients with AF significantly had more hypertension, diabetes mellitus, chronic renal disease, valvular heart disease and congestive heart failure, while patients without AF had more dyslipidaemia and were more likely to be current smokers. Patients with AF had significantly more prevalence of Non-STEMI on presentation and were less likely to receive reperfusion therapy while in-hospital coronary artery bypass surgery was equal between the two groups. There were no differences

between the two groups in peak CK-MB levels or echo-cardio graphic left ventricular ejection fraction.

4.4.3.2. Medications (Table 2)

Prior to admission: Patients with AF were significantly more likely to be on aspirin, warfarin, beta-blockers, calcium channel blockers (CCB), digoxin, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACE/ARB), and antiarrhythmics, when compared to patients without AF.

Admission: Patients with AF were significantly were more likely to be treated with digoxin, warfarin and antiarrhythmics and less likely to be treated with beta-blockers and aspirin.

Discharge: Patients with AF were significantly more likely to be prescribed digoxin, warfarin and antiarrhythmics and less likely to be prescribed aspirin, clopidogrel and beta-blocker. Calcium channel blockers and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers use were comparable between the two groups.

4.4.3.3. In-Hospital Outcomes

Patients with AF had significantly higher in-hospital stroke and mortality rates when compared to patients without AF (table 1). Multivariate predictors of poor outcome among patients hospitalized with AMI were age, female gender and LVEF < 35%. Atrial fibrillation was not an independent predictor of poor outcome (table 3). Age was the only independent predictor of AF in patient with AMI in our study (table 4).

4.4.4. Discussion

The current study demonstrates for the first time 20-years observations of the clinical characteristics and outcome of Middle Eastern Arab and South Asian patients hospitalized with

AMI according to the presence of AF. Patients with AF were significantly older and had more prevalence of hypertension, diabetes mellitus, chronic renal disease, valvular heart disease, congestive heart failure and non-STEMI on presentation while patients without AF had more dyslipidaemia, were more likely to be current smokers and more likely to receive thrombolysis and coronary interventions. Patients with AF had significantly higher in-hospital mortality rate and stroke rates when compared to patients without AF. Age was the only independent predictor of AF in patient with AMI in our study and AF was not independently a predictor of poor outcome.

We report an overall incidence of 1.8% of AF in our AMI patients which is lower than that observed in other studies performed in North America and Europe which showed an incidence ranging from 6% to 15% depending on the cohort of AMI studied [2,11-23] (table5). Sub-analysis according to ethnicity revealed an incidence of 0.8% in South Asians. This very low frequency observed in South Asians is concordant with earlier observations in this ethnicity [3]. Novaro et al performed a meta-analysis which included 1735 Asian patients with AF complicating AMI reported the frequency to be 4.7% [3]. Additionally, a lower prevalence of AF has been consistently observed in Asians in various clinical settings. In a general practice population [24], the AF prevalence in Indo-Asians aged >50 years was 0.6% .In a multi-ethnic hospital registry [25], AF appeared to be less prominently associated with non-haemorrhagic stroke in Indo-Asians compared with whites. In patients newly hospitalized for heart failure [26], AF was less common in South Asians compared with whites (15% vs 31%, $p = 0.0002$). These findings reporting a lower prevalence of AF in Asians in general practice, during an acute stroke, or when presenting with heart failure are consistent with our findings in a post AMI population.

We also report an incidence of 3.1% in Arabs in our cohort. This is consistent with our previous observation from the second Gulf Registry of Acute Coronary Events (Gulf RACE-2) analysis [27], which revealed an incidence of 2.7% of AF in a cohort of patients with acute coronary syndromes from six adjacent Arabian Gulf countries (Bahrain, Saudi Arabia, Qatar, Oman, United Arab Emirates, and Yemen) collected over 9 months.

Consistent with several other reports, patients with AF in our study were more likely to be female than were patients without AF. In a systematic review of the incidence, clinical features, and prognostic implications of AF in AMI, Schmitt et al [2] observed that female gender was a predictor of AF in 7 out of 14 studies; while male gender was associated with AF in 2. In our multivariate analysis, however, female gender was not an independent predictor of AF development in our AMI patients. Reported predictors of AF in the setting of AMI include advancing age, presence of heart failure symptoms, higher heart rates at admission, and left ventricular dysfunction with age being the most commonly reported factor [2]. In our study increased age was actually the only predictor of AF. Considering that the mean age of our AMI cohort was 53 years, which is much lower than that in other registries and AMI studies, this may be the reason behind the very low rates of AF in our study.

Our study demonstrated a significant impact of AF on survival in patients with AMI with increased in-hospital mortality from 7.1% to 20% (P=0.001). AF was not, however, an independent predictor of increased mortality in our cohort of patients. Previous studies showed conflicting results; with some studies showing no significant adverse effect of AF on AMI mortality [11,14,20], while others illustrated an independent adverse effect [13,15,16,18,21]. Nonetheless, a recent meta-analysis of mortality associated with AF in AMI patient by Jabre et al [28] reported that mortality odds ratio associated with AF was 1.46 (95% confidence interval, 1.35 to 1.58; I2=76%; 23 studies). Whether it is an independent predictor of mortality

or not, our findings, combined with previous experience in other regions including different ethnicities, clearly demonstrate a significant impact of this arrhythmia on the survival of patients with AMI.

4.4.5. Conclusions

The results of this 20-years observational study in residents of a Middle-eastern country provide for the first-time insights into the characteristics and in-hospital outcome among AF in the setting of AMI patients from Middle-eastern Arab and South Asians ethnicities. Our findings confirm previous reports in other ethnicities that advancing age is the major independent predictor of AF in AMI patients. Further prospective studies are required evaluating optimal therapeutic approaches for these high-risk patients in order to reduce the high mortality observed.

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4.4.7. Tables

4.4.7.1. Table1. Patients' demographics, clinical characteristics and outcomes comparison between AMI patients with and without AF

Variable	AMI + AF (N=227)	AMI no AF (N=12654)	P Value
Patient characteristics at admission (%)			
Age in year (mean ±SD)	56±12	53±11.9	0.001
Body mass index (kg/m2) (mean ±SD)	29±12.5	27±16	0.27
Gender Female	69(30.4)	1542(12.2)	0.001
Ethnicity (%)			
Middle Eastern Arabs	156(68.7)	5028(39.7)	
South Asians	48(21.1)	5985(47.3)	
Others	23(10.1)	1641(13)	
Age in different ethnicities (mean ±SD)			
Middle Eastern Arabs	69±11	59±13	0.001
South Asians	54±8.7	49±8.8	0.001
Others	59±10	53±12	0.02
Cardiovascular risk factors (%)			
Prior myocardial infarction	58(25.6)	1908(15.1)	0.001
Current smoker	36(15.9)	4463(35.3)	0.001
Hypertension*	120(52.9)	4565(36.1)	0.001
Diabetes mellitus†	114(50.2)	5032(39.8)	0.001
Chronic renal impairment	17(7.5)	368(2.9)	0.001
Dyslipidemia††	25(11)	2680(21.2)	0.001
Other Cardiac Diagnosis			
Congestive Heart failure	51(22.5)	1078(8.5)	0.001
Valvular heart disease	3(1.3)	38(0.3)	0.007
Type of AMI			
STEMI	64(28.2)	7006(55.4)	0.001
Non-STEMI	163(71.8)	5648(44.6)	0.001
In-hospital therapy (%)			
Rate of thrombolysis‡	24(10.6)	4697(37.1)	0.001
Percutaneous coronary intervention	7(3.1)	1338(10.6)	0.001
CABG	10(4.4)	394(3.1)	0.27
Peak CK-MB (mean ±SD)	204±587	243±775	0.49
LVEF (mean ±SD)	39±13	42±11	0.06
Hospital days (mean ±SD)			
CCU stay	3±2.5	3±2	0.05
Total hospital stay	7±5	5±3.5	0.001
In hospital outcome (%)			
Death	46(20.3)	894(7.1)	0.001
Stroke	4(1.8)	38(0.3)	0.001

Data are expressed in numbers (%) of patients unless otherwise indicated.

*Systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, or current antihypertensive treatment. †Patient had been informed of the diagnosis by a physician before admission and for type 1 or 2 diabetes.

†† Total cholesterol >5.2 mmol/L or current use of lipid-lowering agent.

‡Of patients eligible for thrombolysis (ST-elevation myocardial infarction (previously known Q wave MI) or new or presumed left bundle branch block).
CABG = coronary artery bypass graft; CCU = coronary care unit; MI = myocardial infarction; LVEF= left ventricular ejection fraction, STEMI = ST elevation myocardial infarction; NSTEMI = non-ST elevation myocardial infarction.

4.4.7.2. Table 2. Medication received on admission and at discharge (other than thrombolysis) comparison between AMI patients with and without AF

Medications in %	Before Admission			During Admission			At Discharge		
	AMI + AF	AMI no AF	P Value	AMI + AF	AMI no AF	P Value	AMI + AF	AMI no AF	P Value
Aspirin	42.7	24	0.001	75.8	89.9	0.001	67.4	87.8	0.001
Warfarin	0.4	0.0	0.006	8.4	0.6	0.001	18.1	3.1	0.001
Clopidogrel	8.4	6.1	0.17	26.9	29	0.48	22	30.8	0.005
Beta blocker	19.8	8.7	0.001	37.4	47.6	0.002	25.6	32.5	0.03
CCB	8.8	3.2	0.001	7	6.9	0.93	9.7	9.8	0.95
Digoxin	12.3	1.1	0.001	26.4	1.3	0.001	24.2	1.7	0.001
ACE inhibitors/ARBs	18.1	7.6	0.001	33.9	29.1	0.11	41	39.9	0.75
Other Antiarrhythmics	14.1	1.3	0.001	42.7	5.9	0.001	33.9	3.0	0.001

Data are expressed in % of patients.
GP = glycoprotein; LMWH = low molecular weight heparin; CCB = calcium channel blockers;
ACE=angiotensin converting enzyme inhibitor, ARB=angiotensin receptor blocker.

4.4.7.3. Table 3. Multivariate analysis of predictors of in-hospital mortality in AMI patients

Variable	Adjusted OR	95% CI	P-Value
Age	1.04	1.02 – 1.05	0.001
Female gender	2.05	1.40 – 3.13	0.001
Diabetes mellitus	1.12	0.77 – 1.63	0.57
Hypertension	1.10	0.74 – 1.64	0.64
Dyslipidemia	1.22	0.79 – 1.88	0.38
Chronic renal impairment	1.41	0.81 – 2.40	0.23
Current Smoking	0.76	0.50 – 1.18	0.22
EF < 35	5.21	3.70 – 7.43	0.001
Atrial fibrillation	1.82	0.90 – 3.67	0.10

OR= odd ratio; C.I.= confident interval; EF= ejection fraction.

4.4.7.4. Table 4. Multivariate analysis of predictors of AF in AMI patients

Variable	Adjusted OR	95% CI	P-Value
Age	1.06	1.04 – 1.08	0.001
Female gender	1.60	0.94 – 2.70	0.08
Diabetes mellitus	0.88	0.54 – 1.44	0.62
Hypertension	0.81	0.49 – 1.36	0.42
Old MI	1.58	0.94 – 2.66	0.09
Current Smoking	0.57	0.31 – 1.04	0.07
EF < 35	1.14	0.70 – 1.84	0.61

OR= odd ratio; C.I.= confident interval; EF= ejection fraction.

4.4.7.5. Reported studies describing incidence and in-hospital outcome AF after AMI compared to current study

Table 9 Reported studies describing incidence and in-hospital outcome AF after AMI

Author /study	Year	Study characteristics	Total AMI	AF-incidence %	Mean age years		In-hospital mortality%		In-hospital stroke %	
					AF	No AF	AF	No AF	AF	No AF
Behar/Sprint Prognosis[11]	1992	Sprint Registry, evaluation of Nifedipine after AMI, analysis of patients with paroxysmal AF.	5803	9.9	68.3	62.2	25.5	16.3	NA	NA
Madias[12]	1996	Prospective study, trandolapril vs. placebo, inclusion 1990–92, sub analysis on AF in AMI.	517	11.2	67.9	62.2	30.6	16.9	NA	NA
Crenshaw / GUSTO I[13]	1997	GUSTO I, prospective study on thrombolysis in AMI, streptokinase vs. TPA, sub-analysis on AF.	40 891	7.9	67	60	13.8	5.8	3.1	1.3
Eldar/Sprint[14]	1998	Prospective trial in the thrombolytic era vs. retrospective data from pre-	2866	8.9	70	62	NA	NA	3.9	0.6

		thrombolytic era on AF in AMI.								
Pedersen/TRACE[15]	1999	TRACE, prospective study on trandolapril vs. placebo in AMI, inclusion 1990–92, sub-analysis on AF and Aflutter.	6676	15	73.7	67	18	9	NA	NA
Rathore[16]	2000	Retrospective data analysis, inclusion1994–96, Medicare benefitians aged > 65 years with AMI.	106 780	11.3	79.2	76.8	25.3	16	2.8	1.7
Wong/GUSTO III[17]	2000	GUSTO III, prospective trial on reperfusion strategies after AMI, sub-analysis on AF.	13 858	6	71	62	NA	NA	2	1
Pizzetti/GISSI III[18]	2001	GISSI III, prospective trial, ACE-inhibitors vs. Nitrates in otherwise optimal treated patients after AMI.	17 944	6.1	NA	NA	12.6	5	0.8	0.7
Goldberg[19]	2002	Retrospective analysis, inclusion 1990–97, comparison of treatment and outcome changes after AMI and AF.	2596	13.2	73.9	66.3	21.5	10.5	NA	NA
Kinjo/OACIS[20]	2003	OACIS, prospective study on AF after AMI, all patients were treated with PCI.	2475	7.7	69.8	63.4	16	6.7	2.3	0.6
Lehto/OPTIMAAL[21]	2005	OPTIMAAL, prospective study on losartan vs. captopril after AMI with LV-dysfunction	5477	7.2	73.1	66.6	33	15.1	9.2	4.4
Kober/VALIANT[22]	2006	VALIANT, prospective study, AMI patients with LVSD and/or heart	14 703	12.3	71.9	64.6	NA	NA	NA	NA

		failure, valsartan vs. placebo, sub-analysis on AF.								
Jabre[23]	2011	The Rochester Epidemiology Project community-based cohort	3220	6.8	72	65	NA	NA	NA	NA
Current Study	--	Retrospective analysis of a prospective registry in Qatar 1991-2010	12 881	1.8	56	53	20.3	7.1	1.8	0.3

AF= atrial fibrillation, AMI= acute myocardial infarction, CHF= congestive heart failure, CI= confidence interval, NA= not available.

4.5. The prognostic implications of lack of palpitations in patients hospitalised with atrial fibrillation: observations from a 20-year registry

4.5.1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice and is associated with increased risks of stroke, heart failure, dementia, and death [1]. AF and its related symptoms therefore represent a major therapeutic challenge and burden to healthcare systems [2]. It is well recognized that the presentations of AF at the time of first diagnosis vary substantially with palpitations being the most common typical symptom. Other atypical symptoms include chest pain, shortness of breath (SOB) and dizziness [3]. In addition, about 15% to 30% of patients are asymptomatic [4-6]. It is sometimes practiced that when AF is thought to be suppressed, as evidenced by the absence of clinical symptoms and the presence of sinus rhythm on routine electrocardiograms, some physicians tend to stop anticoagulation in an effort to avoid the perceived unnecessary exposure of patients to anticoagulation therapy [7]. Nonetheless, recent evidence from ambulatory external electrocardiogram monitoring and examining implanted device memories have demonstrated that such patients may have asymptomatic recurrences of AF and that these subclinical episodes expose them to the risk of ischemic stroke and other thromboembolic events [8-11], thereby questioning the utility of lack of symptoms as an indicator of lower risk. The aim of this study is to examine the prevalence and prognostic implications of lack of typical symptoms on presentation with AF, namely palpitations, among patients hospitalized with AF and entered into a national registry over a 20-year period.

4.5.2. Materials And Methods

Study setting, definitions and statistical analysis are the same as described in section 4.1.2. [12-17].

4.5.3. Results

From 1991 to end of 2010, a total of 41,438 patients with acute cardiac disease were hospitalized with an overall in-hospital mortality rate of 4.7%. 3850 patients were admitted with AF and 37588 patients were admitted with other cardiovascular diagnoses and no-AF. Of patients hospitalized with AF; 1724 (44.8%) had palpitations on presentation while 2126 (55.2%) had no palpitations. other symptoms were, in order of frequency; shortness of breath (27.8%), chest pain (11.6%), dizziness (6.4%) and non-cardiac symptoms (3.2%) whereas 6.1% of patients were completely asymptomatic.

4.5.3.1. Baseline clinical characteristics and In-Hospital Outcomes [Table 1]

Patients who lacked palpitations were 9 years older, had a higher prevalence of hypertension (HTN), diabetes mellitus (DM), chronic renal impairment (CRD) and underlying coronary artery disease (CAD) (history of Prior myocardial infarction) compared to patients with palpitations. Current smokers' prevalence was significantly higher in patients with palpitations. Acute coronary syndromes (ACS), heart failure (HF) and valvular heart disease (VHD) were significantly more common concomitant cardiac diagnoses in patients without palpitation. There were 141 deaths among the group with no palpitations compared with 19 among the group with palpitations (6.6% versus 1.1%; P= 0.001).

Medication: At the time of admission, patients without palpitation were more likely to be on beta-blockers, calcium channel blockers (CCB), digoxin and other antiarrhythmics compared with patients with palpitation.

Medication On admission: patients with palpitation were more likely to be treated with beta-blockers and other antiarrhythmics on admission while digoxin was prescribed more frequently to patients without palpitations. CCB use was comparable between the 2 groups.

4.5.3.2. Prevalence and Mortality in different patient subsets [table 2]

Lack of palpitations on admission was more common in both males and females than the presence of palpitations. It was also significantly more frequent in patients with concomitant ACS, DM, HTN, chronic renal impairment, prior myocardial infarction, patients with severe left ventricular dysfunction and heart failure whereas palpitations was more common in current smokers. The mortality rates were significantly higher in women and men without palpitations and in patients who had concomitant ACS, DM, HTN, severe left ventricular dysfunction and current smokers.

4.5.3.3. Patients with - lack of palpitations- clinical features and outcomes [Table 3]

Of 2126 in the group of patients with - lack of palpitations-; 1183 had atypical symptoms including SOB, chest pains, dizziness or non-cardiac symptoms and 233 patients were asymptomatic. There were more patients with prior myocardial infarction and dyslipidemia in the atypical symptoms group compared with the asymptomatic group. ACS, HF and VHD were significantly more common concomitant cardiac diagnoses in patients with atypical symptoms. There were no significant differences between the two groups in left ventricular function on echocardiography or in-hospital outcomes.

4.5.3.4. Predictors of -lack of palpitations- [table 4]

Multivariate analysis of predictors of (lack of palpitations) among patients hospitalized with AF were severe left ventricular dysfunction on echocardiography, chronic renal impairment, acute coronary syndrome, and age.

4.5.3.5. Predictors of in-hospital mortality [table 5]

Multivariate analysis of in-hospital mortality predictors identified (lack of palpitations) as an independent predictor of in-hospital mortality (OR 5.56; 95% CI 1.20 – 25.0, p= 0.03) (Table

3). Associated ACS was also a significant predictor of mortality (OR 3.53; 95% CI 1.40 – 8.90, p= 0.007) while angiotensin converting enzyme inhibitor/angiotensin receptor blockers use on admission offered protective effect (OR 0.16; 95% CI 0.05 – 0.55, p= 0.004).

4.5.4. Discussion

The current study represents the largest observational study comparing the impact of symptoms at the presentation with AF on patient outcomes. Patients who lacked palpitations were older and more likely to have cardiovascular risk factors, underlying coronary artery disease and heart failure. The mortality rate of patients without palpitations was significantly higher compared to patients with palpitations. Significantly, the study demonstrates for the first time that the absence of palpitations was an independent predictor of in-hospital mortality. We suspect that this most likely could still be due to confounders, which were significantly more frequent in these patients so that in patients who were admitted in ACS or CHF, the presence of other more severe symptoms may have overshadowed the presence of milder symptoms of palpitations.

Interest in symptomatic status of patients with AF has been stimulated by evidence from major clinical trials in AF management that demonstrated that the outcome of rate versus rhythm control therapies was similar [18-20]. AF symptoms related to the arrhythmia has since become a major consideration during the selection of a treatment strategy. Nonetheless, the relationship of symptoms to meaningful outcomes and prognosis has not been well established [21]. Several studies have demonstrated that approximately 65% of documented AF episodes (pacemaker or trans-telephonic monitoring) are asymptomatic [22-24]. These subclinical AF episodes were recently shown to be associated with a significantly increased risk of ischemic stroke or systemic embolism [10]. The current study complements these observations in that patients who lacked the typical symptoms of AF have higher mortality.

Our study differentiated typical versus atypical symptoms of AF on presentation. Whether our findings can be extrapolated to patients with subclinical AF requires further research. We, and others, have previously reported atypical presentation in acute coronary syndromes to be an independent predictor of in-hospital mortality [25-28]. It is hypothesized that the type and severity of symptoms of myocardial ischemia depend on the type and number of nociceptive afferent nerves activated and these afferent impulses may stimulate efferent impulses in the autonomic nervous system to produce symptoms [29]. Noxious stimuli are differentially modified by neuropathies, neuroreceptors (for example, NK1 and endorphins), and comorbidities (diabetes mellitus) [30-31]. In contrast, the sensory pathways underlying palpitations sensations are poorly understood [3, 32]. For instance, it has been demonstrated that one third of heart transplant recipients were accurately aware of their resting heartbeat despite the absence of cardiac innervations [33]. Possible sensory receptors responsible for heartbeat sensations are myocardial, pericardial, and peripheral mechanoreceptors, and/or peripheral baroreceptors with their afferent parasympathetic and sympathetic pathways [34].

It is possible that in patients who lack palpitations, these sensory receptors may be affected by long-standing arrhythmias with relatively low maximum ventricular rate or by the presence of peripheral neuropathy (e.g., in diabetic patients). This is, however, only a hypothesis and represents an area for future research.

It may also be hypothesized that the worse outcome among patients with lack of palpitations is attributed to the fact that they have worse clinical profile and comorbidities; however even after adjustment of baseline variables, -lack of palpitation- was an independent predictor of worse outcome. Another potential explanation is that patients without palpitations have accommodated to their AF. Younger patients may experience palpitations, but as the disease progresses, they adjust their lifestyles accordingly to avoid situations which increase the

likelihood of palpitations. Hence the non-palpitation patients would tend to be older, sicker, and have more progressed AF. It is worth noting that the Fibrillation Registry Assessing Costs, Therapies, Adverse events and Lifestyle (FRACTAL) Registry of AF did identify palpitations as a more common presenting symptom of AF in younger patients (under the age of 65) compared with dyspnea and fatigue in older patients [35]. The current study suggests the need to further study this association as well as the mechanisms of this worse outcome in the near future.

Additionally, further research is warranted on the clinical application of our findings. Should physicians perform more aggressive monitoring in patients who present with atypical symptoms to look for the presence of AF? Is the lack of palpitations causing these patients to delay seeking care until it is too late? Perhaps devices which monitor other physiologic parameters (e.g., respiration, heart rate, fluid status) may be useful in identifying patients who need medical attention before they get so sick that hospitalization is required.

The current study also highlights the importance of history as a cost-effective prognostic indicator in the evaluation of patients with AF. This is particularly significant as the burden of AF is expected to increase because of several reasons including the aging population and improved survival of patients with coronary artery disease, heart failure and hypertension [36,37]. This will result in increased cost of investigation and treatment of this condition [38,39], and thus such inexpensive prognostic indicators in history evaluation of patients become of increased importance.

4.5.5. Limitations of the study

Despite being one of the largest studies in AF symptomatology conducted so far, the number of deaths in this study was still relatively small. Such an analysis should be, therefore, repeated in future studies to replicate the findings and in other populations and ethnic groups. In

addition, our study differentiated typical versus atypical symptoms of AF on presentation. Whether our findings can be extrapolated to patients with subclinical AF requires further research. Our registry included only patients hospitalized to the cardiology department whereas patients with AF in other departments (e.g., Perioperative AF or AF in other medical intensive care settings) were not included. The analysis included all patients hospitalized with AF, whether it was a primary or secondary diagnosis. The current study included patients hospitalized with AF and whether these findings apply to patients presenting to the outpatient`s setting requires further study. Our study is also constrained by the limitations inherent in all studies of historical, observational design. Inaccuracies in the diagnosis and coding of AF in routine data are well recognized and the possibility of residual confounding. Additionally, temporal changes in referral and coding practices, in diagnostic accuracy, and in awareness of AF as a diagnostic entity may have influenced our findings. Other study limitations could include missing data or measurement errors, possible confounding by variables not controlled for, as this was an observational study. Our study focused on in-hospital outcome and long-term data is not available.

The results of this observational study comparing the impact of symptoms at the presentation with AF on patient outcomes provide for the first-time insights into role of cost-effective history taking in prognosis of patients with AF. To the best of our knowledge the current study is the first ever report demonstrating that -lack of palpitations- is a predictor of in-hospital mortality independent of other risk factors or therapy. Further research is warranted to confirm and explain the mechanisms behind this novel observation and to investigate the utility of this cost-effective prognostic indicator in risk stratification of patients with AF.

4.5.6. Acknowledgments

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4.5.7. References

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4.5.8. Tables

4.5.8.1. Table 1. Atrial fibrillation patients' clinical characteristics and outcomes

Variable	Palpitation (n=1724)	No-palpitation (n=2126)	P Value
Patient characteristics at admission			
Age (years) mean ±SD	51±14.8	60±15	0.001
Body mass index (kg/m2) mean ±SD	30±7.5	29.9±10	0.62
Cardiovascular risk factors			
Current smoker	278(16.1)	199(9.4)	0.001
Hypertension*	591(34.3)	892(42)	0.001
Diabetes mellitus†	408(23.7)	749(35.2)	0.001
Chronic renal impairment	55(3.2)	127(6)	0.001
Dyslipidemia††	153(8.9)	212(10)	0.25
Prior myocardial infarction	107(6.2)	310(14.6)	0.001
Concomitant cardiac diagnoses			
Acute coronary syndrome	64(3.7)	225(10.6)	0.001
Heart failure	131(7.6)	564(26.5)	0.001
Valvular heart disease	54(3.1)	112(5.3)	0.001
Severe LVEF of < 35%	27(6.6)	119(25.5)	0.001
Total hospital stay (days) mean ±SD	3.5±3	5±4.6	0.001
Medications Before Admission			
Beta-Blockers	143(8.3)	228(10.7)	0.01
CCB	61(3.5)	104(4.9)	0.04

Digoxin	235(3.6)	552(26)	0.001
Antiarrhythmics	271(15.7)	597(28.1)	0.001
Medications On Admission			
Beta-Blockers	491(28.5)	404(19)	0.001
CCB	164(9.5)	222(10.4)	0.34
Digoxin	767(44.5)	1052(49.5)	0.002
Antiarrhythmics	1180(68.4)	1237(58.2)	0.001
In hospital outcome			
Death	19(1.1)	141(6.6)	0.001
Stroke	0(0.0)	16(0.8)	0.001

Data are expressed in numbers (%) of patients unless otherwise indicated. SD= standard deviation
*Systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, or current antihypertensive treatment. †Patient had been informed of the diagnosis by a physician before admission and for type 1 or 2 diabetes.
†† Total cholesterol >5.2 mmol/L or current use of lipid-lowering agent.
CCB = calcium channel blockers, LVEF= left ventricular ejection fraction on echocardiography

4.5.8.2. Table 2. Prevalence and Mortality in different patient subsets

Patients subsets (AF +X)	**Number of patients**				**Mortality**		
	TOTAL NUMBER	**Palpitation N (%)**	**No-palpitation N (%)**	**P Value**	**Palpitation**	**No-palpitation**	**P Value**
Women	1417	646(45.6)	771(54.4)	<0.05	7(1.1)	56(7.3)	0.001
Men	2432	1078(44.3)	1354(55.7)	<0.05	12(1.1)	85(6.3)	0.001
Acute coronary syndrome	289	64(22.1)	225(77.9)	0.001	2(3.1)	46(20.4)	0.001
Diabetes mellitus	1157	408(35.3)	749(64.7)	0.001	7(1.7)	69(9.2)	0.001
Hypertension	1483	591(39.9)	892(64.7)	0.001	9(1.5)	69(7.7)	0.001
Chronic renal impairment	182	55(30.2)	127(69.8)	0.001	3(5.5)	19(15)	0.07
Prior myocardial infarction	417	107(25.7)	310(74.3)	0.001	5(4.7)	31(10)	0.09
EF < 35	205	52(25.4)	153(74.6)	0.001	0(0)	12(7.8)	0.04
Heart failure	695	131(18.8)	564(81.2)	0.001	6(4.6)	51(9)	0.09
Current Smoking	477	278(58.3)	199(41.9)	0.001	4(1.4)	15(7.5)	0.001

Data are expressed in numbers (%) of patients unless otherwise indicated, EF= ejection fraction

4.5.8.3. Table 3. Clinical features and outcome of patients with - lack of palpitations- divided into asymptomatic and those with atypical symptoms

Variable	Atypical symptoms	Asymptomatic	P Value
Patient characteristics at admission			
Patients numbers	1893	233	
Age (years) mean ±SD	60±15	59±15	0.55
Body mass index (kg/m2) mean ±SD	30±10	32±9	0.41
Cardiovascular risk factors			
Current smoker	180(9.5)	19(8.2)	0.51
Hypertension	796(42)	96(41.2)	0.81
Diabetes mellitus	679(35.9)	70(30)	0.08
Chronic renal impairment	116(6.1)	11(4.7)	0.40
Dyslipidemia	202(10.7)	10(4.3)	0.002
Prior myocardial infarction	290(15.3)	20(8.6)	0.006
Concomitant cardiac diagnoses			
Acute coronary syndrome	216(11.4)	9(3.9)	0.001
Heart failure	540(28.5)	24(10.3)	0.001
Valvular heart disease	93(4.9)	19(8.2)	0.04
Total hospital stay (days) mean ±SD	5±5	4±4	0.001
In hospital outcome			
Stroke	13(0.7)	3(1.3)	0.32
Death	129(6.8)	12(5.2)	0.34

4.5.8.4. Table 4. Predictors of -lack of palpitations-

Variable	Adjusted OR	95% CI	P-Value
Age	**1.04**	**1.03 – 1.06**	**0.001**
Male gender	1.15	0.82 – 1.63	0.42
Acute coronary syndrome	**2.08**	**1.26 – 3.43**	**0.001**
Diabetes mellitus	1.29	0.88 – 1.89	0.20
Hypertension	1.03	0.70 – 1.51	0.89
Dyslipidemia	0.82	0.50 – 1.35	0.43
Chronic renal impairment	**2.30**	**1.05 – 5.03**	**0.04**
Current Smoking	0.90	0.59 – 1.37	0.61
Prior myocardial infarction	1.33	0.74 – 2.40	0.34
EF < 35	**2.32**	**1.57 – 3.43**	**0.001**
ACE/ARB *	1.10	0.75 – 1.61	0.64
Beta-blockers *	1.12	0.78 – 1.60	0.54
Antiplatelet agents *	0.88	0.61 – 1.28	0.51
Digoxin*	2.13	0.96 – 4.70	0.06
Other Antiarrhythmics *	1.20	0.62 – 2.31	0.60

* Pre-admission medications

ACE/ARB (ACE=angiotensin converting enzyme inhibitor, ARB=angiotensin receptor blockers); CI= confident interval; EF= ejection fraction; OR= odds ratio

4.5.8.5. Table 5. Predictors of in-hospital mortality

Variable	Adjusted OR	95% CI	P-Value
Age	0.99	0.97 – 1.03	0.97
Male gender	0.87	0.34 – 2.23	0.77
Lack of Palpitation on admission	**5.56**	**1.20 – 25.0**	**0.03**
SOB on admission	1.32	0.54 – 3.32	0.55
Acute coronary syndrome	3.53	1.40 – 8.90	0.007
Diabetes mellitus	2.00	0.77 – 5.20	0.15
Hypertension	0.67	0.24 – 1.84	0.43
Dyslipidemia	2.05	0.68 – 6.17	0.20
Chronic renal impairment	2.27	0.75 – 6.89	0.15
Current Smoking	1.03	0.33 – 3.26	0.96
Prior myocardial infarction	1.32	0.49 – 3.57	0.59
EF < 35	3.45	1.14 – 10.00	0.03
ACE/ARB *	0.16	0.05 – 0.55	0.004
Beta-blockers *	0.43	0.17 – 1.08	0.07
Antiplatelet agents *	1.04	0.27 – 3.99	0.96
Digoxin*	0.84	0.17 – 4.24	0.83
Other Antiarrhythmics *	0.50	0.15 – 1.66	0.26

* Administered on admission

ACE/ARB (ACE=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blockers); CI= confident interval; EF= ejection fraction; OR= odds ratio; SOB=shortness of breath

4.6. Impact of religious fasting on the burden of atrial fibrillation: a population-based study

4.6.1. To the editor,

Many of the world's religions recommend periods of fasting and, of these; the Islamic fast during the month of Ramadan is strictly observed worldwide by millions of Muslims. Muslims neither eat nor drink anything from dawn till sunset, a period that varies with the geographical site and the season that in summer months and northern latitudes, the fast can last up to 18 hours or more [1]. Muslims observing the fast must not only abstain from eating and drinking, but also from taking oral medications as well as intravenous fluids and nutrients. In addition, there is associated altered sleep-wake schedule that causes an increase in daytime sleepiness, yet the demands of the daily routine (including religious considerations) reduce the chances that individuals will take a daytime nap to compensate [2]. Fasting during Ramadan is therefore a radical change in lifestyle for the period of one lunar month. The rationale behind the relation of Ramadan fasting and the development of atrial fibrillation (AF) stems from several observations. On one hand, sleep deprivation and eating disturbances have been previously linked to AF and pro-arrhythmia [3,4]. On the other hand favorable changes in lipid profile has been reported in relation to fasting during Ramadan [5] and this may at least in theory result in protection from myocardial ischemia, a known risk factor for AF. Therefore our objective in this study is to investigate whether Ramadan fasting has any effect on the number of hospitalization with AF in the geographically defined population of Qatar.

Qatar is a small Arab country with a population of around 600,000 (2001 Census) and 1,6 million (2010 Census), consisting of Qatari and other Middle-eastern Arabs (less than 40%) as well as other ethnic groups. This study focuses only on Qatari patients rather than expatriates because it is a stable population and avoids the bias in the fluctuation of expatriate population

in the country that varies from time to time. In addition, more than 95% of Qatari adults fast without fail during the month of Ramadan [6]. This study is based at Hamad General Hospital, Doha, Qatar. This hospital provides inpatient and outpatient medical and surgical care for the residents of Qatar; nationals and expatriates where more than 95% of cardiac patients are being treated in the country making an ideal center for population-based studies. The Cardiology and Cardiovascular Surgery Database at Hamad General Hospital was used for this study. Data were collected from the clinical records written by physicians at the time of patient's discharge from the hospital according to predefined criteria for each data point. These records have been coded and registered at the cardiology department since January 1991.

With the described database, we conducted a retrospective review of clinical data study on all Qatari patients in Qatar for a period of 20 years (January 1991 through December 2010) who were hospitalized with AF [table 1]. The study included patients with first hospitalizations as well as recurrences of AF. Patients were divided according to the time of presentation in relation to the month of Ramadan; 1 month before, during and 1 month after Ramadan. The number of hospitalizations for AF in various time periods was analyzed. The age of presentation, gender, cardiovascular risk factor profiles (smoking status, hypertension, hypercholesterolemia, diabetes, pre-existing coronary heart disease) and outcome were analyzed [table 2]. The ethics committee waived the need of informed consent because of its retrospective analysis and the fact that the data was analyzed anonymously.

Of the 41453 patients treated during the 20-year period, 1718 Qatari patients were hospitalized for AF [table 1]. The number of hospitalizations for AF was not significantly different in Ramadan (143 cases) when compared to a month before Ramadan (136 cases) and a month after Ramadan (151 cases); [$p = 0.95$]. There was no significant difference found in the baseline clinical characteristics, presentation, in-hospital stroke or mortality in patients

presenting in various time periods; p = non-significant for all except for patients with history of prior myocardial infarction (MI) were less likely to be hospitalized during Ramadan month (P=0.01). The rate of hospitalizations of patients with underlying myocardial ischemia (as evidenced by concomitant acute coronary syndromes and/or history of old MI) was significantly lower in Ramadan (9.8%) compared to other months (19.1% & 23.2%; P= 0.02) [table 2].

The first finding of our study is that religious fasting has neutral overall effects on the hospitalizations rates with AF during Ramadan. Our findings are concordant with our previous work on Ramadan fasting and the burden of other cardiac disease [7-9], further supporting cardiac safety of fasting. The current study complements these studies and addresses AF that was not previously studied [1]. The second finding of our study is the reduced rate of hospitalizations in Ramadan month of AF with underlying ischemic heart disease (as evidenced by concomitant acute coronary syndromes and/or history of old MI). There are two hypotheses for the reduction of ischemic AF burden during fasting. The first is that the favorable effects on lipid profile during fasting provide protection from myocardial ischemia. We have recently reported significant improvements in high density lipoprotein-cholesterol (HDL-C), and low density lipoprotein-cholesterol (LDL-C) levels in normal healthy fasting individuals during Ramadan that persisted even after four weeks post Ramadan [5]. Similar favorable findings in HDL-C and LDL-C levels were also previously reported in other studies [10-11]. In addition, a significant improvement in 10 years coronary heart disease Framingham risk score and other cardiovascular risk factors including: systolic blood pressure, weight, body mass index and waist circumference in subjects with a previous history of cardiovascular disease has also been reported in addition to favorable lipid profiles [12].

The other hypothesis is related to the favorable effect of catecholamine inhibition that occurs during fasting. Hunger has been associated with catecholamine inhibition (catecholamine surge has been implicated as a trigger for acute coronary syndromes) and reduced venous return, causing a decrease in the sympathetic tone, which leads to a fall in blood pressure, heart rate and cardiac output [13]. Inhibition of catecholamine production during hunger has also been implicated for the heart rate reductions that are observed during Ramadan fasting [14]. Similar findings were also observed in healthy volunteers undergoing moderately heavy aerobic exercise tests during and 1 month after Ramadan [15].

In summary, the current study is the first ever evaluation of the impact of religious fasting on the hospitalizations with AF in a geographically-defined population. Our study demonstrates that fasting has neutral overall effects on AF and suggests a favorable protective effect from ischemic AF. Further research is warranted to investigate the relationship of fasting and myocardial ischemia.

4.6.2. References

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4.6.3. Tables

4.6.3.1. Table 1. Clinical characteristics of the AF cohort under study

	Number (%)
Total hospitalizations (20 years)	41453
AF hospitalizations (20 years)	3850
Qatari	1718
Females	840(48.9)
Males	878(51.1)

AF Qatari	
Mean age	61±16
Hypertension*	812(47.3)
Diabetes mellitus†	673(39.2)
Smokers	128(7.5)
Old MI	236(13.7)
CABG	84(4.9)
In hospital Mortality	101(5.9)

Data are expressed in numbers (%) of patients unless otherwise indicated.
*Systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, or current antihypertensive treatment.
†Patient had been informed of the diagnosis by a physician before admission and for type 1 or 2 diabetes.
AF= atrial fibrillation, CABG = coronary artery bypass graft; MI = myocardial infarction

4.6.3.2. Table 2. Patients' demographics, clinical characteristics and outcomes comparison according to time of presentation

Variable	Month Before Ramadan	Ramadan month	Month After Ramadan	9month Average	P Value
Patient characteristics at admission	136	143	151	143	0.95
Age in year (mean ±SD)	59±18	60±16	61±17	61±16	0.35
Female Gender	65(47.8)	62(43.4)	71(47)	72(49.8)	0.48
Risk factors					
Current smoker	11(8.1)	8(5.6)	10(6.6)	11(7.7)	0.79
Hypertension*	62(45.6)	71(49.7)	71(47)	68(47.2)	0.92
Diabetes mellitus†	48(35.3)	60(42)	61(40.4)	56(39.1)	0.70
Chronic renal impairment	11(8.1)	9(6.3)	9(6.0)	11(7.5)	0.85
Dyslipidemia††	13(9.6)	11(7.7)	15(9.9)	18(12.6)	0.24
Prior myocardial infarction	21(15.4)	10(7)	30(19.9)	19(13.6)	0.01
Concomitant Diagnosis					
Heart failure	30(22.1)	29(20.3)	40(26.5)	34(24.1)	0.60
Valvular heart disease	4(2.9)	5(3.5)	2(1.3)	3(1.9)	0.45
Acute coronary syndrome	9(6.6)	5(3.5)	11(7.3)	12(8.3)	0.21
Underlying myocardial ischemia‡	26(19.1)	14(9.8)	35(23.2)	28(19.6)	0.02
Total hospital stay (mean ±SD)	4±3.9	4±4	4.8±4.7	4.8±4	0.31
In hospital outcome					
Death	11(8.1)	10(7)	7(4.6)	8(5.7)	0.56
Stroke	0(0)	0(0)	1(0.7)	1(0.7)	0.58

Data are expressed in numbers (%) of patients unless otherwise indicated.

*Systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, or current antihypertensive treatment. †Patient had been informed of the diagnosis by a physician before admission and for type 1 or 2 diabetes.

†† Total cholesterol >5.2 mmol/L or current use of lipid-lowering agent.

‡ Prior myocardial infarction and/or acute coronary syndrome on presentation

4.7. Impact of Chronic Kidney Disease on the Presentation and Outcome of Patients Hospitalized with Atrial Fibrillation: Insights from Qatar

4.7.1. Introduction

The prevalence of cardiovascular (CV) disease (CVD) is high among patients with chronic kidney disease (CKD). Most of the patients with CKD die because of CVD rather than progression to end stage renal disease.1 In patients on dialysis, mortality because of CVD is up to 30 times higher compared with the general population [1].

The prevalence and incidence of Atrial Fibrillation (AF) among patients with CKD is also high and is associated with higher morbidity and mortality [2-20]. Moreover, patients with the dual disease have higher incidence of bleeding with warfarin therapy [2,20-22]. The clinical characteristics and outcome of patients on dialysis who have AF has been reported in the medical literature [2-14].

The clinical characteristics and outcome of patients who are hospitalized with AF and coexistent CKD have been reported rarely. In this research, the clinical characteristics and outcome of patients with AF with and without co-existent CKD, hospitalized over a period of 20 years have been reported.

4.7.2. Materials and methods

Study setting, definitions and statistical analysis are the same as described in section 4.1.2. [23-25].

4.7.3. Results

Between 1991 and end of 2012, a total 5201 consecutive patients were hospitalized with AF; 264 (5.1%) patients had CKD.

4.7.3.1. Patient symptoms and baseline clinical characteristics (table1)

Patients with CKD presenting with AF were, on an average, 9 years older than patients with normal renal function. Compared with patients without CKD, CV risk factors were significantly more prevalent in CKD patients including hypertension, DM, and old myocardial infarction whereas smoking was more prevalent in patients with normal renal function. Patients with CKD were significantly more likely to present with shortness of breath and chest pain compared with patients without CKD. Palpitation was significantly more common in patients with normal renal function. Other concomitant cardiac diagnosis at the time of admission including ACS and heart failure were significantly more prevalent in CKD patients while there was no difference in valvular heart disease (p=0.6). In patients who underwent echocardiography, left ventricular (LV) dysfunction was significantly more frequent in patients with CKD while normal LV ejection fraction was significantly more frequent in patients with normal renal function.

4.7.3.2. Medications (Table 2)

At the time of admission; CKD patients were more likely to be on aspirin, clopidogrel, Beta-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB), calcium channel blockers, digoxin and other antiarrhythmics. Warfarin use was comparable between the two groups.

Admission: CKD patients were more likely to be treated with aspirin, clopidogrel, and calcium channel blockers and less likely to be treated with antiarrhythmics. There was no preference in

the use of anticoagulation with warfarin, nor heparin (both unfractionated and low molecular weight heparins), beta-blockers and ACEI/ARB between the two groups.

Discharge: there was no significant difference in the prescription of warfarin or aspirin between the two groups on discharge. CKD patients were more likely prescribed clopidogrel beta-blockers, antiarrhythmics, and calcium channel blockers whereas ACE/ARB were significantly more prescribed to patients without CKD. Digoxin use was used comparably between the 2 groups.

4.7.3.3. Outcomes (Figures 1,2)

In-hospital stay (mean ± SD) was significantly longer for patients with CKD compared with patients without CKD (6.3±4.3 vs 4.5±3.6 days, p=0.001). Compared with patients without CKD, patients with CKD had significantly higher crude in-hospital mortality (11.7 vs 4.0%, p=0.001) and stroke [2.3- vs 0.3%, p=0.001], [Figure 1]. On multivariate analysis, independent predictors of in-hospital mortality were: CKD [Odds Ratio (OR) 2.84 ; 95% confidence interval (CI) 1.33 to 6.08, p=0.001], ACS [OR 2.97 (95% CI 1.67 to 5.30, p=0.001)], left ventricular ejection fraction (LVEF) ≤ 40% [OR 2.44 ; 95% CI 1.41-4.35, p=0.001] and DM [OR 1.96 ; 95% CI 1.03-3.70, p=0.04], [Figure 2].

4.7.4. Discussion

The present study analyses the clinical characteristics and outcome of patients admitted to our hospital, over a period of 22 years, with AF with and without co-existent CKD. Of all the patients admitted with AF, 5.1% had CKD. The patients with coexistent AF and CKD were older, had higher prevalence of cardiovascular co-morbidities and LV dysfunction compared with patients with AF but without CKD. Moreover, the incidence of stroke during hospitalization was 7 times higher and mortality was 3 times higher in patients with AF and coexistent CKD compared with patients with AF alone.

4.7.4.1. Baseline characteristics

In patients on dialysis, the clinical characteristics and outcome of patients with co-existent AF have been fairly well reported in literature (table 3) [2-14]. Mlodawska et al. analyzed the data of 1523 patients who were hospitalized with AF in Poland between 2012 and 2014 [15]. They reported that the prevalence of CKD was 31% among these patients. Other investigators reported a prevalence of CKD between 22.5% to 38% among patients with AF from different countries who were being followed in outpatient clinics or were enrolled in clinical trials [16-19]. The cohort of Olesen et al., comprised of stable patients who were discharged from a hospital with a diagnosis of AF [20]. Among the patients with AF, 3.4% had co-existent CKD. Patients who died within a month of hospital discharge were excluded from that study.

The present study described the clinical characteristics of all patients admitted to the hospital as a case of AF over a period of 22 years. Moreover, the baseline clinical characteristics, presenting symptoms, medications and outcomes were separately studied and reported in the minority of patients with co-existent CKD and compared with that of patients with AF alone. Compared with the patients in the study reported by Olesen et al., the patients in the present study were probably sicker since they were hospitalized [20].

In patients with AF, palpitation and shortness of breath has been described as the predominant symptoms, followed by dizziness and lastly, chest pain [26-28]. In the present study, palpitation and shortness of breath were the most common presenting symptoms which agrees with other studies. The interesting feature was that on segregating the patients on the basis of presence or absence of CKD, it was noted that palpitation was the most common presenting symptom in patients with AF alone while shortness of breath was the commonest presenting symptom in those with AF and coexistent CKD. The incidence of dizziness was quite low in both groups in the study.

In the cohort of Olesen et al., the prevalence of systemic hypertension as well as CHF in the two groups were similar to that noted in the present study [20]. However, the prevalence of DM was much lower in the cohort of Olesen et al. (22.6% in patients with dual disease and 8.6% in patients with AF alone) [20]. This is probably because of the higher prevalence of DM in our region.

4.7.4.2. Medications used

In the cohort of Olesen et al., aspirin was used in 23% patients with dual disease and in 18.7% patients with AF alone ($p<0.001$), while warfarin was used in 17.5% patients with dual disease and 28.6% in patients with AF alone ($p<0.001$).20

Sun et al. reported that among patients attending outpatient clinics because of AF in mainland China, the use of warfarin among eligible patients was significantly lower among those with CKD (36%) compared with those without CKD (38.5%, $p = 0.018$) [17]. The use of Non-Vitamin K Antagonists (NVKA) was similar among those with moderate CKD as well as those with normal estimated Glomerular Filtration Rate (eGFR) values. Barrios and coworkers reported that among patients with AF attending primary health care in Spain, the use of anticoagulant therapy among eligible patients was significantly lower among those with AF and CKD compared with those with AF alone [18]. Similarly, Wu and colleagues reported that among patients with AF enrolled in the German Patient Database, the use of anticoagulant therapy decreased as the eGFR worsened [19]. Among patients eligible for chronic anticoagulation, more than half of those with severe CKD and around quarter of those with moderate CKD were not receiving anticoagulant therapy.

In the present study, the use of warfarin was similar among patients with AF with or without CKD. NVKAs were not available during the period when this study was conducted.

4.7.4.3. Mortality and outcome

Vazquez et al. reported that in patients on dialysis, the presence of AF was associated with 4.6 to 17 times increased risk for thromboembolism compared with dialysis patients without AF [3,5,7]. Olesen et al. reported incident CVA as 3.61, 6.44 and 5.61 cases/100 patient years in patients with AF and normal kidneys, AF with moderate CKD and AF with End Stage Renal Disease (ESRD), respectively [20]. Piccini et al. analyzed data from a large multinational clinical trial which included patients with AF who were at moderate to high risk for thromboembolism [29]. They reported that adding creatinine clearance <60 ml/min to CHADS2 or the CHA2 DS2 VASc scheme resulted in a significant improvement in stroke risk assessment in patients with AF. In contrast, Banerjee et al. reported that addition of renal impairment did not improve the predictive capacity of CHADS2 or CHA2 DS2 VASc scores based on data of patients with AF in a particular community [30].

In the present study, the incidence of stroke in patients hospitalized for AF was 7 times higher in patients with concomitant CKD compared with those with AF alone. To the best of our knowledge, there was no other study which reported incidence of acute stroke in patient hospitalized for AF.

In the present study, mortality during hospitalization was 3 times higher in patients with dual disease. In the cohort of Mlodawska et al., in hospital mortality was 2.7 times higher among patients who were hospitalized with non-valvular AF and had coexistent CKD compared with those with non-valvular AF without CKD [15].

In the present study, after adjustment for multiple variables, CKD, LVEF ≤40%, and ACS were independent predictors of mortality in patients hospitalized with AF. The influence of CKD and ACS on mortality was much higher than that observed with diabetes. Genovesi et al. reported a similar association in a cohort of HD patients with AF [9]. In the cohort of

Mlodawska et al., age >70 years, CKD and chronic heart failure were independent predictors of in hospital mortality among patients hospitalized for non-valvular AF [15].

4.7.5. Conclusion

Around 5% patients hospitalized with AF had CKD. These patients with AF and CKD had higher cardiovascular co-morbidities. These patients had 7 times higher risk for developing acute stroke and 3 times higher risk for death during hospitalization compared with patients with AF alone. In patients with AF, the presence of CKD, LV dysfunction and ACS are strong predictors of mortality independent of other co-morbidities.

Hospitalized patients with AF and CKD are probably the sicker ones. Identifying factors associated with poor outcomes in this patient population can provide insight for better management of these patients.

4.7.6. References

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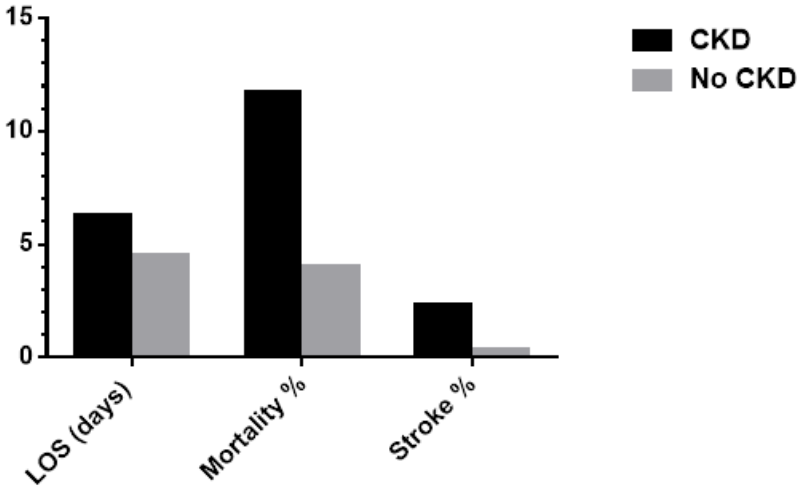
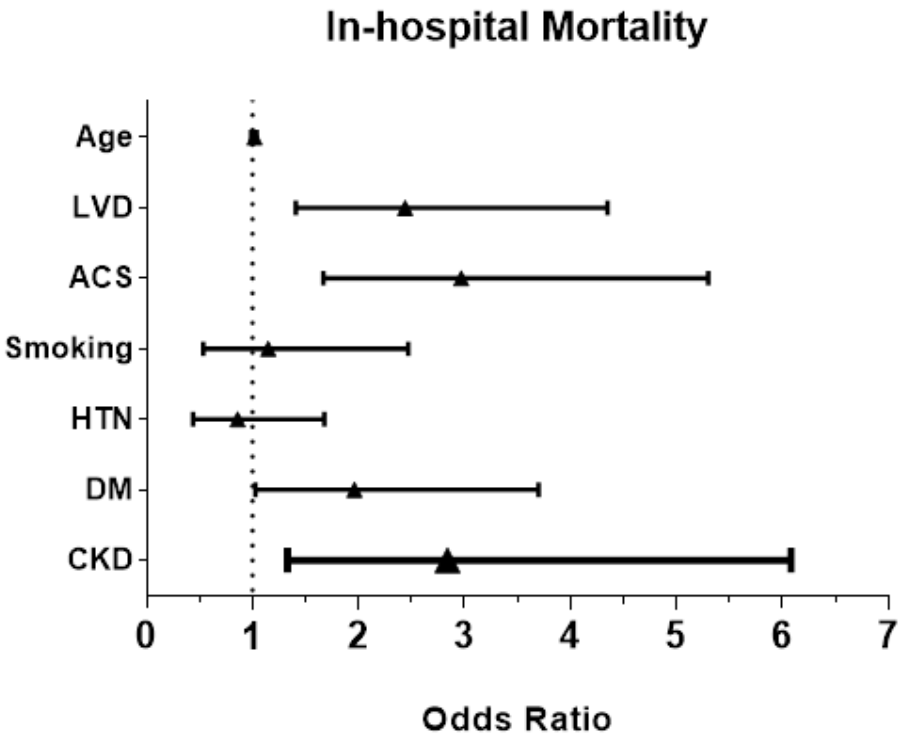
4.7.7. Figures

4.7.7.1. FIGURE 1. In-hospital Outcomes



CKD = chronic kidney disease, LOS = Length of stay (mean, days)

4.7.7.2. FIGURE 2. Odds ratio and 95% confidence intervals for in-hospital mortality



LVD = left ventricular dysfunction (≤40%), ACS = acute coronary syndromes, HTN = hypertension, DM = diabetes mellitus, CKD = chronic kidney disease.

4.7.8. Tables

4.7.8.1. Table1. Patient features, symptoms and clinical characteristics in CKD vs non-CKD patients with atrial fibrillation

Variable	AF + CKD (n = 264, 5.1%)	AF + No CKD (n = 4937, 94.9%)	p
Patient characteristics at admission			
Age (years) (mean ± SD)	67±12	56±15	0.001
Body mass index (kg/m^2) (mean ± SD)	30.8±8.0	29.8±7.0	0.50
Cardiovascular risk factors			
Current smoker	17(6.4)	663(13.4)	0.001
Hypertension*	197(74.6)	1990(40.3)	0.001
Diabetes mellitus†	153(58)	1527(30.9)	0.001
Dyslipidemia††	13(4.9)	218(4.4)	0.69
Prior myocardial infarction	53(20.1)	518(10.5)	0.001
Presenting symptom			
Palpitation	74(28)	2177(44.1)	0.001
Dizziness	8(3.0)	333(6.7)	0.02
Chest pain	17(6.4)	169(3.4)	0.01
SOB	137(51.9)	1420(28.8)	0.001
Other Cardiac Diagnosis			
Acute coronary syndrome	54(20.5)	503(10.2)	0.001
Heart failure	85(32.2)	868(17.6)	0.001
Valvular heart disease	7(2.7)	227(4.6)	0.14
Peak CK-MB Median (IQR)	5.5(2.8-17.8)	3.6(2.3-8.8)	0.77
Left ventricular ejection fraction			
>50%	31(33.3)	797(53.9)	
40-50%	14(15.1)	193(13.0)	
< 40%	48(51.6)	490(33.1)	0.001

Data are expressed in numbers (%) of patients unless otherwise indicated.
*Systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg, or current antihypertensive treatment. †Patient had been informed of the diagnosis by a physician before admission and for type 1 or 2 diabetes.
†† Total cholesterol >5.2 mmol/L or current use of lipid-lowering agent.
SOB = shortness of breath.

4.7.8.2. Table2. Medication received before, during admission and at discharge in AF with CKD vs non-CKD patients

Medications	Before Admission			During Admission			At Discharge		
	CKD	No CKD	p	CKD	No CKD	p	CKD	No CKD	p
Aspirin	150 (56.8)	1467 (29.7)	0.001	174 (65.9)	2550 (51.7)	0.001	153 (58)	2698 (54.6)	0.29
Warfarin	3 (1.1)	69 (1.4)	0.72	48 (18.2)	940 (19.0)	0.73	79 (29.9)	1688 (34.20	0.15
Clopidogrel	33 (12.5)	214 (4.3)	0.001	46 (17.4)	431 (8.7)	0.001	43 (16.3)	364 (7.4)	0.001
Beta-blocker	64 (24.2)	631 (12.8)	0.001	72 (27.3)	1466 (29.7)	0.40	86 (32.6)	1985 (40.2)	0.01
CCB	32 (12.1)	270 (5.5)	0.001	62 (23.5)	523 (10.6)	0.001	80 (30.3)	604 (12.2)	0.001
Digoxin	25 (9.5)	230 (4.7)	0.001	-	-	-	26 (9.80)	373 (7.6)	0.17
ACE inhibitors/ARBs	44 (16.7)	622 (12.6)	0.05	68 (25.8)	1457 (29.5)	0.19	67 (25.4)	1635 (33.1)	0.009
Unfractionated heparin	-	-	-	70 (26.5)	1259 (25.5)	0.71	-	-	-
LMWH (enoxaparin)	2 (0.8)	16 (0.3)	0.24	29 (11.0)	721 (14.6)	0.10	1(0.4)	37 (0.7)	0.49
Antiarrhythmics	45 (17)	365 (7.40	0.001	58 (22.0)	1040 (21.1)	0.73	77 (29.2)	939 (19.0)	0.001

Data are expressed in percentages (%) of patients, CKD = Chronic Kidney Disease, GP = glycoprotein; LMWH = low molecular weight heparin; CCB = calcium channel blockers; ACE = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker.

4.7.8.3. AF in Patients with Chronic Kidney Disease as Reported in the Literature

Table 10 AF in Patients with Chronic Kidney Disease as Reported in the Literature

Author	Year	Aim of study	Type of study	n of patients	Conclusions and highlights
Vazquez et al.[3]	2000	To determine the prevalence of AF in pts on hemodialysis and to evaluate its influence on development of thromboembolic complications.	Observation study over one year.	190	AF was seen in 13.6% pts on HD. Mortality was 23% in patients with AF as compared to 6% in patients in sinus rhythm. Thromboembolic event was seen in 35% patients with AF as compared to 4% patients in sinus rhythm.

Wiesholzer et al.[4]	2001	To assess the incidence of CVA in pts on hemodialysis and to evaluate the impact of AF and other potential risk factors for its development in this population.	Retrospective analysis of medical records from 1975 to 1997.	430	Incidence of CVA in patients with CKD and AF, without anticoagulation, did not differ statistically from that in patients with CKD and without AF. Incidence of CVA was higher in patients with diabetic nephropathy, age > 65 years, moderate to severe HTN, weight gain > 2 kg between dialysis and antiplatelet or warfarin therapy.
Va´zquez et al.[5]	2003	To evaluate long term impact of AF on clinical outcomes in patients on hemodialysis.	Observational study over 4 years.	190	Presence of AF was associated with high mortality in patients on hemodialysis over 4 years follow up.
Genovesi et al.[6]	2005	To assess the prevalence of AF and associated risk factors in pts on long term hemodialysis.	Observational study over 6 months.	488	AF was more frequent in patients on HD. Old age, long term HD, left atrial enlargement were commonly associated with AF.
Castroviejo et al.[7]	2006	To determine incidence of AF in hemodialysis patients, determine risk factors and assess its clinical implications.	Long term observational study over 7 years.	164	Each year 3% patients developed AF. AF was associated with 5 fold increase in thromboembolic complications. Development of AF was not an independent predictor of mortality.
Atar I et al. [8]	2006	To determine the incidence of AF in patients with ESRD on hemodialysis and to determine the risk factors for AF in this population.	Observational study.	275	AF is common in patients with ESRD. Patients with AF were older. Incidence of hypertension, CAD, LV dysfunction, right atrial diameter and mitral and aortic valve calcification was higher. Serum albumin and HDL was significantly lower in patients with AF.
Genoves et al.[9]	2008	1. To assess the relation between AF, age, duration of hemodialysis and other co morbid conditions and all cause and cardiovascular mortality. 2. To assess the relation between ACE inhibitors and co morbid conditions with new onset AF. 3. To assess the relation between AF and co morbid illness with hospitalizations. In patients with ESRD on hemodialysis.	Observational study of patients on hemodialysis in 5 centers in Italy over 3 years.	476	1. Patients with AF had greater total and cardiovascular mortality. 2. Hospital admissions were more in patients with AF. 3. New onset AF was less in patients on ACE inhibitors. 4. New onset AF was higher in presence of LVH on ECG.
Vazquez et al.[10]	2009	To estimate the prevalence and incidence of AF and its impact on ischemic CVA and all-cause mortality in hemodialysis patients over a period of 4 years.	Observational study over 4 years.	256.	Prevalence of AF was noted in 12.1% patient at the onset and incidence of 12.4% over 4 year follow up. Presence of valvular calcification, bundle branch blocks, previous CVA, low EF, high pulse pressure and low hemoglobin were associated with higher risk for developing AF. AF increased mortality by 1.72 and CVA risk by 9.8 fold.

Wizemann et al.[11]	2010	To determine the incidence, prevalence and outcome of AF in patients on hemodialysis.	Observation study involving data analysis of DOPPS study.	17,513	Advanced age, non-black race, higher facility mean dialysate calcium, prosthetic heart valves and valvular heart disease were associated with an increased risk for developing new onset AF. All-cause mortality and CVA was higher in patients with AF at enrolment.
Soliman et al.[12]	2010	To determine the prevalence of AF among patients with CKD enrolled in CRIC study.	Observational study.	3,267	AF was detected in 18% of study population and in 25% pts >70 years.
Chou et al.[13]	2010	To determine the prognosis and outcome in ESRD pts with paroxysmal AF, permanent AF and paroxysmal AF converted to permanent AF.	Retrospective longitudinal study from Jan 2001 to Dec 2007.	81 patients with paroxysmal AF 49 pts with perm AF 89 patients with paroxysmal to permanent AF.	Patients' survival was not different in the three groups. Thromboembolism was significantly higher in patients with paroxysmal AF.
Wetmore et al.[14]	2012	To determine the prevalence of AF in patients on hemodialysis in USA, eligible for federal assistance.	Observation study involving Medicare and Medicaid database analysis.	63,884	Prevalence of AF was 7%. Age >60 years, male, Caucasians, BMI >25kg/m2, CAD, CHF were significantly associated with AF. Prevalence of AF in younger patients was much higher than that reported for age-matched group not on hemodialysis.
Olesen et al.[20]	2012	To determine the risk of stroke or systemic thromboembolism and bleeding associated with CKD in patients with AF.	Retrospective analysis of Danish national registries to identify patients discharged from hospital with non-valvular AF between 1997 and 2008.	132,372	CKD was associated with increased risk of stroke or systemic thromboembolism and bleeding among patients with AF. Warfarin was associated with reduction in incidence of stroke or thromboembolism and increase in bleeding among patients with CKD.
Mlodawska et al.[15]	2014	To assess renal parameters among patients hospitalized with AF and to study the association between eGFR values and different types of AF and in hospital mortality.	Retrospective analysis of data of 1523 patients who were hospitalized with AF in Poland between 2012 – 2014.	1523	In hospital mortality was 2.7 times higher among patients with AF and CKD [OR 2.7 (95% CI: 1.34-5.61, p=0.06)]. On multivariate regression analysis, in patients with AF, the odds for in hospital mortality was higher if age > 70 years CKD and Chronic Heart Failure.
Present study		To assess the presentation, clinical features, treatment and outcome of patients hospitalized with AF and CKD.	Retrospective analysis of clinical record of patients hospitalized with AF between 1991 and 2012.	5201	Patients hospitalized with AF and coexistent CKD have higher cardiovascular co- morbidities and poor clinical outcome.

AF = Atrial Fibrillation, BMI = Body Mass Index, CAD = Coronary Artery Disease, CHF = Congestive Heart Failure, CKD = Chronic Kidney Disease, CVA = Cerebro Vascular Accident, DM = Diabetes Mellitus, eGFR = estimated Glomerular Filtration Rate, ESRD = End Stage Renal Disease, ECG = Electrocardiogram, GFR = Glomerular Filtration Rate, HD = Hemodialysis, HDL = High Density Lipoprotein, LV = Left Ventricular, LVH = Left Ventricular Hypertrophy

5. Supplementary Tables

Literature search on 26/09/2020

WHO regions

- WHO South-East Asia region: Bangladesh, Bhutan, India, Indonesia, Maldives, Myanmar, Nepal, Sri Lanka, Thailand, and Timor.
- WHO Eastern Mediterranean region: Afghanistan, Bahrain, Djibouti, Egypt, Iran, Iraq, Jordan, Kuwait, Lebanon, Libya, Morocco, Oman, Pakistan, Palestine, Qatar, Saudi Arabia, Somalia, Sudan, Syria, Tunisia, United Arab Emirates, and Yemen.

5.1. Table S1. Search strategy

Table S1. Search strategy

	Database	**Records**
	EMBASE - 1st set	
#1	'atrial fibrillation'/exp OR 'atrial fibrillation' OR ('fibrillation'/exp OR fibrillation))	175,817
#2	arab*	343,518
#3	arab	87,482
#4	middle AND eastern	20,209
#5	middle AND east*	79,645
#6	south AND asian	49,105
#7	south AND asia*	98,099
#8	#1 AND #2	1,288
#9	#1 AND #5	545
#10	#1 AND #7	730
#11	#8 OR #9 OR #10 (('atrial fibrillation'/exp OR 'atrial fibrillation' OR (atrial AND ('fibrillation'/exp OR fibrillation))) AND arab*) OR (('atrial fibrillation'/exp OR 'atrial fibrillation' OR (atrial AND ('fibrillation'/exp OR fibrillation))) AND (middle AND east*)) OR (('atrial fibrillation'/exp OR 'atrial fibrillation' OR (atrial AND ('fibrillation'/exp OR fibrillation))) AND (south AND asia*))	**2,421**
	EMBASE - 2nd set	
#1	('atrial fibrillation'/exp OR 'atrial fibrillation' OR (atrial AND ('fibrillation'/exp OR fibrillation)))	174,815

#2	Bangladesh* OR bhutan* OR india* OR indonesia* OR maldives* OR myanmar* OR nepal* OR ‘sri lanka’ OR ‘sri lankan’ OR thailand* OR thai OR timor	1,588,554
#3	afghan* OR bahrain* OR djibouti* OR egypt* OR iran* OR iraq* OR jordan* OR kuwait* OR lebanon* OR lebanese OR libya* OR morocc* OR oman* OR pakistan* OR qatar* OR ‘saudi arabia’ OR ‘saudi arabian’ OR saudi OR somalia* OR sudan* OR syria* OR tunisia* OR ‘united arab emirates’ OR uae OR yemen*	1,024,567
#4	#1 AND #2 AND #3 (('atrial fibrillation'/exp OR 'atrial fibrillation' OR (atrial AND ('fibrillation'/exp OR fibrillation))) AND (bangladesh* OR bhutan* OR india* OR indonesia* OR maldives* OR myanmar* OR nepal* OR 'sri lanka' OR 'sri lankan' OR thailand OR thai OR timor) AND (afghan* OR bahrain* OR djibouti* OR egypt* OR iran* OR iraq* OR jordan* OR kuwait* OR lebanon OR lebanese OR libya* OR morocc* OR oman* OR pakistan* OR qatar* OR 'saudi arabia' OR 'saudi arabian' OR saudi OR somalia* OR sudan* OR syria* OR tunisia* OR 'united arab emirates' OR uae OR yemen*)	**282**
	Sub-total	**2,703**
	PubMed	
	atrial fibrillation[MeSH Terms]	55,862
	((((atrial fibrillation[MeSH Terms])) AND (arabs[MeSH Terms])) OR (middle eastren[MeSH Terms])) OR (south asians[MeSH Terms])	**6050**
	("Atrial Fibrillation"[Mesh]) AND "Afghanistan"[Mesh]	1
	("Atrial Fibrillation"[Mesh]) AND "Bahrain"[Mesh]	1
	("Atrial Fibrillation"[Mesh]) AND "Djibouti"[Mesh]	0
	("Atrial Fibrillation"[Mesh]) AND "Egypt"[Mesh]	6
	("Atrial Fibrillation"[Mesh]) AND "Iran"[Mesh]	20
	("Atrial Fibrillation"[Mesh]) AND "Iraq"[Mesh]	0
	("Atrial Fibrillation"[Mesh]) AND "Jordan"[Mesh]	2
	("Atrial Fibrillation"[Mesh]) AND "Kuwait"[Mesh]	2
	("Atrial Fibrillation"[Mesh]) AND "Lebanon"[Mesh]	3
	("Atrial Fibrillation"[Mesh]) AND "Libya"[Mesh]	0
	("Atrial Fibrillation"[Mesh]) AND "Morocco"[Mesh]	4
	("Atrial Fibrillation"[Mesh]) AND "Oman"[Mesh]	3
	("Atrial Fibrillation"[Mesh]) AND "Pakistan"[Mesh]	15
	("Atrial Fibrillation"[Mesh]) AND "Palestine"[-]	0
	("Atrial Fibrillation"[Mesh]) AND "Qatar"[Mesh]	9
	("Atrial Fibrillation"[Mesh]) AND "Saudi Arabia"[Mesh]	7

	("Atrial Fibrillation"[Mesh]) AND "Somalia"[Mesh]	0
	("Atrial Fibrillation"[Mesh]) AND "Sudan"[Mesh]	0
	("Atrial Fibrillation"[Mesh]) AND "Syria"[Mesh]	1
	("Atrial Fibrillation"[Mesh]) AND "Tunisia"[Mesh]	11
	("Atrial Fibrillation"[Mesh]) AND "United Arab Emirates"[Mesh]	2
	("Atrial Fibrillation"[Mesh]) AND "Yemen"[Mesh]	1
	("Atrial Fibrillation"[Mesh]) AND "Bangladesh"[Mesh]	4
	("Atrial Fibrillation"[Mesh]) AND "Bhutan"[Mesh]	0
	("Atrial Fibrillation"[Mesh]) AND "Indonesia"[Mesh]	1
	("Atrial Fibrillation"[Mesh]) AND "Myanmar"[Mesh]	0
	("Atrial Fibrillation"[Mesh]) AND "Nepal"[Mesh]	3
	("Atrial Fibrillation"[Mesh]) AND "Sri Lanka"[Mesh]	3
	("Atrial Fibrillation"[Mesh]) AND "Timor-Leste"[Mesh]	0
	("Atrial Fibrillation"[Mesh]) AND "Thailand"[Mesh]	24
	("Atrial Fibrillation"[Mesh]) AND "India"[Mesh]	43
	Sub-total	**6,216**
	CENTRALE	
#1	MeSH descriptor: [Atrial Fibrillation] explode all trees	4,567
#2	MeSH descriptor: [Arabs] in all MeSH products	47
#3	middle east*	5,706
#4	south asia*	3,376
#5	#1 AND #2	0
#6	#1 AND #3	27
#7	#1 AND #4	8
#8	5 OR #6 OR #7	35
	Sub-total	**35**
	Total	**8,954**

5.2. Table S2. Excluded studies

Table S2. Excluded studies

No.	Study	Reason for exclusion
1.	Islam MS, Islam MA, Azad AK, et al. Use of Anticoagulant Warfarin in Patients Presenting With Atrial Fibrillation in a Tertiary Level Hospital. *Mymensingh Med J*. 2016;25(3):523-529.	Inaccessible
2.	Chowdhury KS, Siddiqui MN. Etiological pattern of atrial fibrillation. *Mymensingh Med J*. 2002;11(2):100-103.	Inaccessible
3.	Sobhy MA, Khoury M, Almahmeed WA, et al. The atrial FibriLlatiOn real World management registry in the Middle East and Africa: design and rationale. *J Cardiovasc Med (Hagerstown)*. 2020;21(9):704-710.	Design and rationale of new registry
4.	Karthikeyan G, Ananthakrishnan R, Devasenapathy N, et al. Transient, subclinical atrial fibrillation and risk of systemic embolism in patients with rheumatic mitral stenosis in sinus rhythm. *Am J Cardiol*. 2014;114(6):869-874.	Subclinical atrial fibrillation
5.	Soni A, Karna S, Fahey N, et al. Age-and-sex stratified prevalence of atrial fibrillation in rural Western India: Results of SMART-India, a population-based screening study. *Int J Cardiol*. 2019;280:84-88.	Technology-assisted atrial fibrillation screening
6.	Soni A, Karna S, Patel H, et al. Study protocol for *S*martphone *M*onitoring for *A*trial fibrillation in *R*eal-*T*ime in India (SMART-India): a community-based screening and referral programme. *BMJ Open*. 2017;7(12):e017668. Published 2017 Dec 14.	Technology-assisted atrial fibrillation screening Study design
7.	Shin SY, Lip GYH. Community screening for atrial fibrillation in the era of smart devices. *Int J Cardiol*. 2019;280:95-96.	Smart device Editorial
8.	Singh B. Nonvalvular atrial fibrillation in India-time to pause, think, and change!. *Indian Heart J*. 2018;70(6):767-768.	Editorial
9.	von Falkenhausen AS, Sinner MF. Atrial fibrillation in Iran: Familiar findings in familial AF. *Int J Cardiol*. 2020;314:75-76.	Editorial
10.	Naik D S, Pillai VM, Adole PS. Comparison of 10-mg and 5-mg warfarin initiation nomograms in a South Indian population - An open label trial. *Thromb Res*. 2019;176:33-35.	Management of atrial fibrillation and venous thromboembolism
11.	Mayet AY, Alsaqer AI, Alhammad AM, Al-Omar HA. Rivaroxaban prescribing in a Saudi tertiary care teaching hospital. *Saudi Pharm J*. 2018;26(6):775-779.	Not on atrial fibrillation alone
12.	El Ghousain HE, Thomas M, Varghese SJ, Hegazi MO, Kumar R. Long term oral anticoagulant therapy with warfarin: experience with local patient population in kuwait. Indian J Hematol Blood Transfus. 2014;30(2):111-119.	Not on atrial fibrillation alone

13.	Priksri W, Rattanavipanon W, Saejear W, et al. Incidence, risk factors, and outcomes of warfarin-associated major bleeding in Thai population. *Pharmacoepidemiol Drug Saf*. 2019;28(7):942-950.	Non-atrial fibrillation indication
14.	Rezaian GR, Poor-Moghaddas M, Kojuri J, Rezaian S, Liaghat L, Zare N. Atrial fibrillation in patients with constrictive pericarditis: the significance of pericardial calcification. Ann Noninvasive Electrocardiol. 2009 Jul;14(3):258-61.	Surgical patients
15.	Safaie N, Maghamipour N, Jodati AR, Mahmoodpoor A, Dashtaki L, Hakimzadeh M. New procedure for treatment of atrial fibrillation in patients with valvular heart disease. *Acta Med Iran*. 2010;48(5):337-341.	Surgical procedure
16.	Hu WS, Hsieh MH, Lin CL. Comparisons of changes in the adapted diabetes complications severity index and CHA2DS2-VASc score for atrial fibrillation risk stratification in patients with type 2 diabetes mellitus: A nationwide cohort study. *Int J Cardiol*. 2018;269:122-125.	Comparisons between risk scores
17.	Rattanachotphanit T, Limwattananon C, Waleekhachonloet O, Limwattananon P, Sawanyawisuth K. Cost-Effectiveness Analysis of Direct-Acting Oral Anticoagulants for Stroke Prevention in Thai Patients with Non-Valvular Atrial Fibrillation and a High Risk of Bleeding. *Pharmacoeconomics*. 2019;37(2):279-289.	Cost-effectiveness
18.	Dilokthornsakul P, Nathisuwan S, Krittayaphong R, Chutinet A, Permsuwan U. Cost-Effectiveness Analysis of Non-Vitamin K Antagonist Oral Anticoagulants Versus Warfarin in Thai Patients With Non-Valvular Atrial Fibrillation. *Heart Lung Circ*. 2020;29(3):390-400.	Cost effectiveness
19.	Hersi AS, Osenenko KM, Kherraf SA, Aziz AA, Sambrook RJ. Cost-effectiveness of apixaban for stroke prevention in non-valvular atrial fibrillation in Saudi Arabia. *Ann Saudi Med*. 2019;39(4):265-278.	Cost-effectiveness
20.	Srinonprasert V, Ratanasumawong K, Thongsri T, et al. Factors associated with low health-related quality of life among younger and older Thai patients with non-valvular atrial fibrillation. *Qual Life Res*. 2019;28(8):2091-2098.	Quality of life
21.	Ben Rejeb O, Brahim W, Ghali H, Ernez S, Mahdhaoui A, Jeridi G. Évaluation de la qualité de l'anticoagulation au long cours par antivitamine-K dans la fibrillation auriculaire [Evaluation of the quality of long-term anticoagulation therapy with antivitamin-K in atrial fibrillation]. *Ann Cardiol Angeiol (Paris).* 2019;68(2):80-86.	Quality of oral anticoagulation
22.	Ouali S, Mechri M, Ben Ali Z, et al. Factors associated to adequate time in therapeutic range with oral vitamin K antagonists in Tunisia. Tunis Med. 2019;97(1):113-121.	Quality of oral anticoagulation Not on atrial fibrillation alone
23.	Mohammed S, Aljundi AH, Kasem M, Alhashemi M, El-Menyar A. Anticoagulation control among patients with nonvalvular atrial fibrillation: A single tertiary cardiac center experience. J Adv Pharm Technol Res. 2017;8(1):14-18.	Quality of oral anticoagulation

24.	Farsad BF, Abbasinazari M, Dabagh A, Bakshandeh H. Evaluation of Time in Therapeutic Range (TTR) in Patients with Non-Valvular Atrial Fibrillation Receiving Treatment with Warfarin in Tehran, Iran: A Cross-Sectional Study. J Clin Diagn Res. 2016;10(9):FC04-FC06.	Quality of anticoagulation
25.	Zubaid M, Saad H, Ridha M, et al. Quality of anticoagulation with warfarin across Kuwait. Hellenic J Cardiol. 2013;54(2):102-106.	Quality of anticoagulation
26.	Knowledge of, satisfaction with and adherence to oral anticoagulant drugs among patients in King Fasial hospital; Taif, Kingdom Saudi Arabia. Elbur A.I., Albarraq A.A., Maugrabi M.M., Alharthi S.A. Int J Pharm Sci Rev Res. 2015;31(1):274-280.	Patient survey about knowledge
27.	Ben Halima A, Aouadi S, Bejjar D, et al. Hypertension and Atrial Fibrillation: What is the prevalence of obstructive sleep apnea syndrome?. *Tunis Med*. 2018;96(3):187-192.	On obstructive sleep apnea
28.	Chandriah H, Kumolosasi E, Islahudin F, Makmor-Bakry M. Effectiveness and safety of a 10mg warfarin initiation nomogram in Asian population. Pak J Pharm Sci. 2015;28(3):927-932.	Oral anticoagulation nomogram effectiveness
29.	Abdelnabi M, Almaghraby A, Saleh Y, et al. Frequency of de novo atrial fibrillation in patients presenting with acute ischemic cerebrovascular stroke. *Egypt Heart J*. 2020;72(1):18.	Region not defined

5.3. Table S3. Co-morbidities and risk factors in atrial fibrillation patients

Table S3. Co-morbidities and risk factors in AF patients

First author	HF	HTN	DM	Prior stroke	CAD/ IHD	VHD	CKD	Smoking	HAS-BLED	CHA_2DS_2-VASc	$CHADS_2$	$CHADS_2$ 0	$CHADS_2$ 1	$CHADS_2$ ≥2
Middle Eastern countries														
Single-center studies														
Al-Turaiki et al, 2016 [7]	17.8%	79.5%	54.5%	14.4%	24.2%$^{\Delta}$	-	18.9%	-	1.98	3.5	2.0	5.0%	24.0%	71.0%
Anouassi et al, 2020 [8]	45.6%	79.4%	52.8%	23.0%	34.5%$^{\Delta}$	-	36.8% (CrCl <60)	-	-	3.8	-	**	**	**
Balaghi-Inalou et al, 2018 [9]	38.3%	78.3%	36.7%	11.7%	-	-	-	-	-	-	-	-	-	-
Ben Rejeb et al, 2019 [10]	14.0%	-	12.0%	17.5%	3.5%	-	-	-	1.2	2.6	-	-	-	-
Bin Salih et al, 2011[11]	26.2%$^{\bullet}$	59.3%	68.3%	7.9%$^{\bullet}$	23.1%	23.6%	-	-	-	-	-	-	-	-
Elkhatib et al, 2020 [12]	-	53.3%	39.3%	20.7%	-	-	-	22.7%	-	-	-	-	-	-
Garadah et al, 2011 [13]	-	38.0%	35.0%	-	21.0%	-	21.0%	39.0%	-	-	-	-	-	-
Mashat et al, 2019 [16]	37.1%	73.1%	53.3%	-	-	58.7%	-	-	-	-	-	-	-	-
Qanash et al, 2011 [17] **Paroxysmal vs. persistent**	33.3% / 38.1%	80.0% / 81.0%	53.3% / 47.6%	33.3% / 38.1%	-	-	-	-	-	-	-	5.6%	83.3%	13.9%
Ridha et al, 2005 [19]	27.5%	65.8%	53.3%	15.8%	55.8%	-	-	-	-	-	-	-	-	-
Sadeghi et al, 2015$^{\Diamond}$ [20]	51.0%	71.0%	25.0%	37.0%	55.0%	-	-	34.0%	2.8	4.3	-	-	-	-
Shatoor et al, 1998 [21]	53.0%$^{\bullet}$	23.7%	18.3%	14.6%$^{\bullet}$	24.3%	26.0%	-	-	-	-	-	-	-	-

First author	HF	HTN	DM	Prior stroke	CAD/ IHD	VHD	CKD	Smoking	HAS-BLED	CHA_2DS_2-VASc	$CHADS_2$	$CHADS_2$ 0	$CHADS_2$ 1	$CHADS_2$ ≥2
Multi-center studies														
AlAwwa et al, 2020[$] [22]	27.8%	83.3%	55.6%	-	33.3%	5.6%	HD pts	11.1%	-	-	-	-	-	-
Al-Radeef MY, 2019 [23]	44.0%	89.0%	30.0%	20.0%	52.0%	-	-	42.0%	-	4.1	2.3	5.0%	26.0%	69.0%
Haq et al, 2009 [24]	27.0%	54.0%	24.0%	11.0%	47.0%	54.0%	-	60.0% (Male)	-	-	-	-	-	-
Ullah et al, 2015 [25]	26.0%	38.0%	-	-	27.0%	9.0%	-	-	-	-	-	-	-	-
Non-AF registries														
Ajlan et al, 2018 [26]	78.0%	70.8%	55.9%	15.0%	42.3%	-	32.9%	11.6%	-	-	-	-	-	-
Hersi et al, 2012 [27]	20.2%	65.9%	44.2%	13.4%	32.7%[Δ]	6.0%	8.8%	68.7%	-	-	-	-	-	-
Imam et al, 2020 [28]	2.0%	72.3%	67.7%*	12.7%	21.1%	2.8%	-	-	-	-	-	-	-	-
Ragbaoui et al, 2017 [29]	100%	55.0%	39.0%	-	-	-	-	26.0%	-	-	-	-	-	-
Cardiology and Cardiovascular Surgery Database														
Dabdoob et al, 2007 [45]	-	40.5%	35.3%	-	-	-	-	-	-	-	-	-	-	-
Salam et al, 2013 [46] **F vs. M**	18.8%[□] / 17.6%	49.5% / 32.1%	37.5% / 25.7%	-	8.3% / 12.3%	3.3%[□] / 6.1%	6.0% / 4.0%	1.3% / 18.9%	-	-	-	-	-	-
Salam et al, 2013 [47] **ME vs. SA**	20.0%[□] / 12.4%	41.7% / 28.2%	34.6% / 17.7%	-	11.9% / 9.5%	3.7%[□] / 6.8%	5.7% / 1.6%	11.3% / 13.9%	-	-	-	-	-	-
Salam et al, 2013 [48]	22.5%[□]	52.9%	50.2%	-	25.0%	1.3%[□]	7.5%	15.9%	-	-	-	-	-	-

First author	HF	HTN	DM	Prior stroke	CAD/ IHD	VHD	CKD	Smoking	HAS-BLED	CHA_2DS_2-VASc	$CHADS_2$	$CHADS_2$ 0	$CHADS_2$ 1	$CHADS_2$ ≥2
Salam et al, 2013 [49]	24.1%□	47.2%	39.1%	-	13.6%	1.9%□	7.9%	7.7%	-	-	-	-	-	-
Salam et al, 2014 [50] **Palpitation vs. none**	7.6%□ / 26.5%	34.3% / 42.0%	23.7% / 35.2%	-	6.2% / 14.6%	3.1%□ / 5.3%	3.2% / 6.0%	16.1% / 9.4%	-	-	-	-	-	-
Salim et al, 2018 [51] **CKD vs. none**	32.2%□ / 17.6%	74.6% / 40.3%	58.0% / 30.9%	-	20.1% / 10.5%	2.7%□ / 4.6%	5.1% / 94.9%	6.4% / 13.4%	-	-	-	-	-	-
AF registries														
Heidarali et al, 2020 [31] **Familial vs. none**	5.3%ΔΔ / 1.3%ΔΔ	25.0% / 26.0%	6.0% / 7.0%	-	13.0% / 16.0%	8.0% / 8.0%	-	14.0% / 17.0%	0 / 0	1.0 / 1.0	-	-	-	-
Hersi et al, 2015 [32]	31.7%	63.2%	48.0%	9.0%	28.5%	-	-	23.0%	-	-	-	-	-	-
Gulf SAFE registry														
Domek et al, 2020 [53] **DM vs. none**	33.3% / 25.1%	81.4% / 40.4%	-	33.3% / 25.1%	47.0% / 20.3%	-	10.7% / 4.2%	-	1.5 / 0.95	3.6 / 1.7	2.6 / 1.0	-	-	-
Domek et al, 2020 [54] **DM pts**	33.5%	81.3%	100%	14.9%	47.1%	-	10.6%	-	1.5	3.6	-	-	-	-
Gumprecht et al, 2020 [55]	27.6%	52.7%	29.8%	11.8%	28.6%	-	6.0%	23.0%	1.1	2.3	-	-	-	-
Li et al, 2019 [56]	25.9%	56.6%	31.7%	11.7%	32.0%Δ	-	-	-	-	2.0	1.0	-	-	-
Miyazawa et al, 2019 [57] **Stroke vs. none**	33.8% / 34.0%	68.3% / 50.2%	35.9% / 28.9%	-	44.3%Δ / 31.8%	-	-	21.7% / 23.0%	-	5.2 / 2.3	3.7 / 1.2	-	-	-

First author	HF	HTN	DM	Prior stroke	CAD/ IHD	VHD	CKD	Smoking	HAS-BLED	CHA_2DS_2-VASc	$CHADS_2$	$CHADS_2$ 0	$CHADS_2$ 1	$CHADS_2$ ≥2
Shehab et al, 2017 [58] **F vs. M**	14.0% / 21.7%	58.1% / 47.3%	32.3% / 27.1%	14.5%^ / 11.3%	26.3% / 29.9%	21.0% / 17.6%	-	6.8% / 37.4%	-	-	-	23.2% / 33.4%	28.1% / 26.9%	48.7% / 39.7%
Zubaid et al, 2011 [33]	27.0%	52.0%	30.0%	13.0%^	28.0%	24.0%	-	23.0%	-	-	-	28.5%	27.5%	44.0%
Zubaid et al, 2015# [59]	26.8%	59.2%	32.7%	13.0%^	32.1%	15.6%	-	23.8%	-	-	1.6	25.0%	27.1%	47.1%
South Asian countries														
Single-center studies														
Bhardwaj et al, 2012 [34]	7.2%ΔΔ	10.2%	5.0%	-	-	5.1%°	-	-	-	-	-	-	-	-
Dhungel et al, 2017 [35] **NVAF**	56.5%	30.5%	-	-	13.6%	14.9%	1.3%	-	-	-	-	-	-	63.6%
Srisilpa et al, 2020 [36] **Dead vs. survive**	9.3% / 6.9%	75.0% / 65.5%	31.2% / 25.2%	25.0% / 25.2%	18.7% / 17.2%	-	9.3% / 3.4%	3.1% / 16.0%	3.4 / 3.2	5.8 / 4.8	-	-	-	-
Multi-center studies														
Apiyasawat et al, 2015 [37]	12.3%	18.2%	15.0%	0.6%	-	-	1.8%	-	-	1.8	-	-	-	-
Krittayaphong et al, 2016 [38]	-	100%	27.7%	-	-	-	-	5.7%	-	-	-	-	-	-
Non-AF registries														
Negi et al, 2018 [39]	15.9%	-	-	4.5%	-	-	-	-	-	-	-	-	-	-
AF registries														
Charantharayil et al, 2019 [40]	26.5%	53.8%	34.5%	14.9%!	34.8%	-	10.3%	-	1.6	2.9	-	-	-	-

First author	HF	HTN	DM	Prior stroke	CAD/ IHD	VHD	CKD	Smoking	HAS-BLED	CHA_2DS_2-VASc	$CHADS_2$	$CHADS_2$ 0	$CHADS_2$ 1	$CHADS_2$ ≥2
Krittayaphong et al, 2018 [41]	27.2%	67.8%	24.1%	17.8%^	15.7%	-	-	-	1.5	3.0	1.8	14.9%	29.7%	55.4%
Krittayaphong et al, 2020 [60]	26.0%	68.4%	24.0%	17.6%^	13.5%	-	-	19.7%	-	-	-	-	-	-
Krittayaphong et al, 2019 [61] **Older vs. younger**	26.3% / 28.5%	75.4% / 56.0%	24.8% / 23.1%	19.3% / 14.1%	18.0% / 12.1%	-	-	-	-	-	-	-	-	-
Narasimhan et al, 2016 [42]	25.9%	50.8%	20.4%	9.5%	23.4%	40.7%	-	18.6%	-	-	-	27.2%	36.2%	36.7%
Sawhney et al, 2018 [43]	15.5%	68.5%	36.2%	9.1%	28.1%	-	5.2%	16.0%	1.5	2.9	-	-	-	-
Vora et al, 2017 [44]	18.7%	31.4%	16.1%	9.1%	5.4%	53.0%&	4.5%	-	$$	-	-	11.6%	19.9%	68.5%§

a Sub continental divided into Indians (53.4%) and South Asians (46.6%)

Δ Reported as vascular disease (not defined)

** Reported CHA_2DS_2-VASc scores: 0-1 = 14.4%, 2-3 = 30.4%, ≥ 4 = 55.2%

◊ Stroke patients

● Reported for acute conditions at the time of AF diagnosis (i.e., congestive HF, acute complication of stroke, TIA, limb ischemia, or combinations)

$ Haemodialysis patients

Δ Includes prior history of myocardial infarction and premature CAD

* Includes diabetics and pre-diabetics

^ Includes stroke and transient ischemic attack

□ Reported as concomitant cardiac diagnoses

Non-valvular atrial fibrillation patients (Gulf SAFE)

ΔΔ Reported dilated cardiomyopathy (DCM)

○ Other than rheumatic heart disease (RHD) which was in 61.3%

& Includes rheumatic (47.6%) and non-rheumatic (5.4%) valvular diseases

$$ Reported scores percentages: 0 = 17.1%, 1 = 33.3%, 2 = 18.9%, ≥ 3 = 30.7%

§ Reported $CHADS_2$ scores of 2 and 3 only

! Includes stroke/transient ischemic attack or systemic embolism

CAD; coronary artery disease, CKD; chronic kidney disease, CrCl; creatinine clearance, DM, diabetes mellitus, F; female, Fam; familial, HD; haemodialysis patients, HF; heart failure, HTN; hypertension, IHD; ischemic heart disease, M; male, ME; Middle Eastern, NVAF; non-valvular atrial fibrillation, SA; South Asian, SC; sub continental, VHD; valvular heart disease.

5.4. Table S4. AF types and symptoms at presentation

Table S4. Atrial fibrillation types and symptoms at presentation

First author	Valvular AF	NVAF	New onset	Paroxysmal	Persistent	Long-standing persistent	Permanent	Acute	Chronic	Palpitation	Dyspnea	Chest pain	Dizziness or syncope	Fatigue
Middle Eastern countries														
Single-centre studies														
Anouassi et al, 2020 [8]	0%	100%	-	-	-	-	-	-	-	-	-	-	-	-
Bin Salih et al, 2011 [11]	-	-	-	-	-	-	-	21.8%	78.1%	24.5%	59.3%	13.4%	6.2%	-
Garadah et al, 2011 [13]	-	-	59.0%	13.0%$^{\Delta}$	-	-	28.0%	-	-	48.0%	14.0%	12.0%	6.0%	-
Qanash et al, 2011 [17]	-	-	-	41.6%	58.4%	-	-	-	-	-	-	-	-	-
Ridha et al, 2005 [19]	-	-	-	-	-	-	-	31.7%$^{\circ}$	68.3%$^{\bullet}$	-	-	-	-	-
Shatoor et al, 1998 [21]	-	-	-	-	-	-	-	39.7%	60.3%	37.0%	56.6%	31.1%	11.9%	-
Multi-centre studies														
Al-Radeef MY, 2019 [23]	-	-	-	27.0%	26.0%	15.0%	32.0%	-	-	97.0%	68%	90.0%	70.0%	78.0%
Haq et al, 2009 [24]	-	-	27.0%	48.0%	-	-	-	-	25.0%	48.0%	36.0%	38.0%	18.0%	5.0%
Non-AF registries														
Hersi et al, 2012 [27]	-	-	0.6%	-	-	-	-	-	-	-	-	-	-	-
Cardiology and Cardiovascular Surgery Database														

First author	Valvular AF	NVAF	New onset	Paroxysmal	Persistent	Long-standing persistent	Permanent	Acute	Chronic	Palpitation	Dyspnea	Chest pain	Dizziness or syncope	Fatigue
Salam et al, 2014 [50]	-	-	-	-	-	-	-	-	-	44.8%	27.8%	11.6%	-	-
Salim et al, 2018 [51] **CKD vs. none**	-	-	-	-	-	-	-	-	-	28.0% 44.1%	51.9% 28.8%	6.4% 3.4%	3.0% 6.7%	-
AF registries														
Heidarali et al, 2020 [31] **Familial vs. none**	-	-	3.6% 1.6%	70.8% 78.0%	17.6% 15.4%	-	8.0% 5.0%	-	-	76.1% 68.5%	20.4% 20.7%	0% 1.4%	17.7% 11.8%	3.5% 3.7%
Hersi et al, 2015* [32]	-	-	13.0%	24.5%	17.5%	-	45.0%	-	-	21.3%	20.5%	-	20.5%	13.3%
Gulf SAFE registry														
Shehab et al, 2017 [58] **F vs. M**	-	-	29.9% 43.5%	17.4% 16.9%	9.7% 9.2%	-	39.7% 27.0%	-	-	-	-	-	-	-
Zubaid et al, 2011[$] [33]	-	-	37.0%	17.0%	10.0%	-	33.0%	-	-	-	-	-	-	-
Zubaid et al, 2015[#] [59] **NVAF pts**	-	84%[§]	41.8%	19.1%	9.0%	-	26.6%	-	-	-	-	-	-	-
South Asian countries														
Single-centre studies														
Bhardwaj et al, 2012 [34]	-	-	-	-	41.6%	-	58.4%	-	-	-	-	-	-	-
Dhungel et al, 2017 [35]	24.9%	75.1%	-	55.2%	34.4%	-	10.4%	-	-	27.3%	42.9%	-	1.3%	1.3%

First author	Valvular AF	NVAF	New onset	Paroxysmal	Persistent	Long-standing persistent	Permanent	Acute	Chronic	Palpitation	Dyspnea	Chest pain	Dizziness or syncope	Fatigue
NVAF vs. valvular				7.8%	41.2%		51.0%			29.4%	35.3%		2.0%	2.0%
AF registries														
Charantharayil et al, 2019 [40]	26.7%	73.3%	-	39.4%	14.4%	-	46.2%	-	-	-	-	-	-	-
Krittayaphong et al, 2018 [41]	-	100%	2.3%	31.1%	19.4%	-	47.2%	-	-	-	-	-	-	-
Krittayaphong et al, 2020 [60]	-	100%	-	33.5%	18.7%	-	47.8%	-	-	-	-	-	-	-
Krittayaphong et al, 2019 [61] **Older vs. younger**	-	100%	-	31.5% / 36.5%	19.2% / 19.7%	-	49.3% / 44.0%	-	-	-	-	-	-	-
Narasimhan et al, 2016[&] [42]	-	-	14.3%	28.7%	22.7%	-	34.3%	-	-	55.0%	66.0%	21.0%	23.1%	48.7%
Sawhney et al, 2018 [43]	-	100%	64.6%[□]	16.4%	10.4%	-	8.5%	-	-	-	-	-	-	-
Vora et al, 2017 [44]	-	-	11.0%	20.4%	33.0%	-	35.1%	-	-	-	-	-	-	-

Δ Reported as recurrent atrial fibrillation

○ Reported as paroxysmal or persistent atrial fibrillation (PPAF)

● Reported as chronic atrial fibrillation (CAF) that included permanent or long-standing persistent

* Reported EHRA classes: class I = 47.4%, class II = 34.8%, class III = 15.7%, class IV = 2.1% (data was available for 325 patients of the 400 patients)

$ Patients with lone AF accounted for 19.0%

Patients with unknown AF type accounted for 3.5%

& Patients with lone AF accounted for 8.1%. Mean time since AF diagnosis was 6.5 months (for all patients)

§ 84% of the total registry sample size

□ Included new and unclassified types

AF; atrial fibrillation, CKD; chronic kidney disease, NVAF; non-valvular atrial fibrillation

5.5. Table S5. AF management

Table S5. Atrial fibrillation management

First author	BB	CCB	Digoxin	Amiodarone	Other AA	VKA	NOACs	Aspirin	Clopidogrel	Rate control	Rhythm control	ECV	Pharm CV	Ablation
Middle Eastern countries														
Single-centre studies														
Al-Turaiki et al, 2016 [7]	-	-	-	-	-	100%^	-	-	-	-	-	-	-	-
Anouassi et al, 2020 [8]	-	-	-	-	-	-	100%*	-	-	-	-	-	-	-
Qanash et al, 2011 [17] **Paroxysmal vs. persistent**	-	-	-	-	-	60.0% / 81.0%	-	40.0% / 14.3%	-	-	-	-	-	-
Sadeghi et al, 2015 [20]	-	-	-	-	-	22.0%	-	44.0%	8.0%	-	-	-	-	-
Multi-centre studies														
AlAwwa et al, 2020 [22]	27.8%	22.2%	-	-	-	-	-	-	-	-	-	-	-	-
Al-Radeef MY, 2019 [23]	-	-	-	-	-	Some pts	-	Most pf pts	-	-	-	-	-	-
Haq et al, 2009# [24]	77.0%	55.0%	81.0%	22.0%	-	72.5% 0% on admission	-	75.0%	-	-	-	●●	●●	-
Ullah et al, 2015 [25]	-	-	-	-	-	○○	○○	16.8%▪	13.4%▪	-	-	-	-	-
Non-AF registries														
Ajlan et al, 2018& [26]	77.7%	-	35.2%	4.7%	-	51.0%	-	55.7%	-	-	-	-	-	-
Hersi et al, 2012# [27]	60.8%	-	-	-	-	-	-	97.2%	64.5%	-	-	-	-	-

First author	BB	CCB	Digoxin	Amiodarone	Other AA	VKA	NOACs	Aspirin	Clopidogrel	Rate control	Rhythm control	ECV	Pharm CV	Ablation
Imam et al, 2020 [28]	-	-	-	-	-	**	**	-	-	-	-	-	-	-
Cardiology and Cardiovascular Surgery Database														
Salam et al, 2013[&] [46] **F vs. M**	10.1% 9.4%	6.7% 2.8%	26.9% 16.7%	-	29.3% 18.6%	1.8% 1.6%	-	31.2% 25.0%	2.9% 2.5%	-	-	-	-	-
Salam et al, 2013[&] [47] **ME vs. SA**	9.2% 11.1%	4.6% 3.5%	48.9% 43.6%	-	25.4% 14.6%	1.5% 2.2%	-	29.5% 21.2%	2.9% 2.6%	-	-	-	-	-
Salam et al, 2013[&] [48]	19.8%	8.8%	12.3%	-	14.1%	0.4%	-	42.7%	8.4%	-	-	-	-	-
Salam et al, 2014[&] [50] **Palpitation vs. none**	8.3% 10.7%	3.5% 4.9%	3.6% 26.0%	-	15.7% 28.1%	-	-	-	-	-	-	-	-	-
Salim et al, 2018[&] [51] **CKD vs. none**	24.2% 12.8%	12.1% 5.5%	9.5% 4.7%	-	17.0% 7.4%	1.1% 1.4%	-	56.8% 29.7%	12.5% 4.3%	-	-	-	-	-
AF registries														
Heidarali et al, 2020 [31] **Familial vs. none**	40.0% 45.0%	8.0% 9.0%	4.4% 5.0%	7.8% 8.0%	50.8% 42.9%	22.0% 24.0%	46.5% 45.0%	13.0% 14.4%	3.5% 3.2%	-	-	54.0% 45.4%	40.7% 33.8%	34.0% 29.8%
Hersi et al, 2015[#] [32]	66.0%	20.8%	30.3%	42.3%	57.7%	38.5%	-	35.5%	1.5%[$]	66.2%	12.0%	11.6%	-	3.8%
Gulf SAFE registry														
Domek et al, 2020[&] [53] **DM vs. none**	56.1% 55.9%	13.2% 5.6%	31.5% 36.0%	-	-	55.6% 49.8%	-	59.6% 49.3%	16.2% 8.1%	-	-	-	-	-

First author	BB	CCB	Digoxin	Amiodarone	Other AA	VKA	NOACs	Aspirin	Clopidogrel	Rate control	Rhythm control	ECV	Pharm CV	Ablation
Domek et al, 2020[&] [54]	56.1%	24.4%	31.7%	8.8%	2.3%	55.7%	-	59.7%	16.3%	-	-	-	-	-
Gumprecht et al, 2020[&] [55]	58.3%	16.3%	36.1%	9.2%	3.1%	51.9%	-	54.4%	11.0%	-	-	-	-	-
Shehab et al, 2017[#] [58] **F vs. M**	37.8% 33.3%	16.4% 10.7%	25.6% 17.4%	-	-	36.8% 25.1%	-	41.3% 38.9%	7.5% 8.0%	-	-	1.1% 2.2%	8.2% 14.4%	-
Zubaid et al, 2015[#] [59]	-	-	-	9.0%	4.0%	27.7% - 59.7%[§]	-	§§	§§	65%	22.0%	2.0%	13.0%	-
South Asian countries														
Single-centre studies														
Bhardwaj et al, 2012 [34]	√	-	√	-	-	98.5%	-	-	-	-	-	-	-	-
Dhungel et al, 2017 [35] **NVAF vs. valvular**	-	-	-	-	-	25.3% 62.7%	-	66.9% 27.5%	-	-	-	-	-	-
AF registries														
Charantharayil et al, 2019[&] [40]	30.9%	-	22.2%	7.4%	0.8%	42.4%	1.9%	19.5%	16.9%	-	-	-	-	-
Krittayaphong et al, 2018[&] [41]	-	-	-	-	-	90.9%	9.1%	ΔΔ	ΔΔ	-	-	-	-	-
Krittayaphong et al, 2020[&] [60]	-	-	-	-	-	68.7%	6.9%	&&	&&	87.8%	12.2%	-	-	-
Krittayaphong et al, 2019[&] [61]	-	-	-	-	-	74.4%	7.0%	□□	□□	-	-	-	-	-

First author	BB	CCB	Digoxin	Amiodarone	Other AA	VKA	NOACs	Aspirin	Clopidogrel	Rate control	Rhythm control	ECV	Pharm CV	Ablation
Older vs. younger						59.1%	6.5%							
Narasimhan et al, 2016[&] [42]	38.5%	24.9%	31.9%	37.2%	3.3%	##	##	##	##	46.1%	35.2%	-	-	-
Sawhney et al, 2018 [43]	-	-	-	-	-	~40.0%	~6.0%	$$	$$	-	-	-	-	-
Vora et al, 2017[&] [44]	21.0%	15.0%	27.0%	17.0%	1.0%	70.0%	3.9% (as other)	23.0%	13.1%	75.2%	-	-	-	-

^ Warfarin use was an inclusion criteria

* A study on NOACs use: apixaban 56.9%, rivaroxaban 22.9% and dabigatran 20.2%

& Medications before hospital admission (baseline)

In-hospital medications

●● Reported as cardioversion in 9.0%

○○ Reported as received anticoagulation in 27.5% of patients who were candidates for anticoagulation based on $CHA2DS_2$-VASc score ≥2 or mitral stenosis with AF (n = 149; represents 72.7% of total patients (n = 205))

▪ Percentage of 149 patients who were candidate for anticoagulation

** On admission only 45.5% of acute stroke patients with known AF were on anticoagulation of which 67% was with warfarin

$ Reported as other antiplatelet agents

§ Medication upon discharge. Use increased with increasing $CHADS_2$ score. Use of dual and triple antithrombotic therapy with antiplatelet agent(s) was 24-45% and 2.0-6.0%, respectively, depending on the $CHADS_2$ scores as well.

§§ Medication upon discharge. Antiplatelet agents use as per $CHADS_2$ scores; 55.3% (score of 0), 48.0% (score of 1), and 34.1% (score of ≥2)

ΔΔ Reported as antiplatelets use (26.5%)

&& Reported as antiplatelet use (24.8%)

□□ Reported as antiplatelet use 25.6% vs. 28.0%

Use according $CHADS_2$ score: oral anticoagulants (38.1% - 47.1%; use decreased with increasing scores), antiplatelet agents (23.1 – 58.1%; use increased with increasing scores), dual therapy (3.8 – 15.2%; use increased with increasing scores)

$$ Antiplatelet therapy was taken by ~40% of patients

AA; antiarrhythmic agents, BB; beta-blockers, CCB; calcium channel blockers, CKD; chronic kidney disease, DM, diabetes mellitus, ECV; electrical cardioversion, Pharm CV; pharmacological cardioversion, F; female, M; male, ME; Middle Eastern, NOACs; non-vitamin K oral anticoagulation, SA; South Asian, VKA; vitamin K antagonists.

5.6. Table S6. Outcomes in AF patients

Table S6. Outcomes in atrial fibrillation patients

First author	Mortality					CVA or TIA	Hospitalization	Major bleeding	F/U period
	In-hospital	30-day	1-year	2-year	3-year				
Middle Eastern countries									
Single-centre studies									
Al-Turaiki et al, 2016 [7]	-	-	-	-	-	-	-	35.6%◊	-
Anouassi et al, 2020 [8]	-	-	-	-	-	9.9%Δ / 3.1%	-	11.7%• / 6.0%	241 days
Ben Rejeb et al, 2019 [10]	-	-	-	-	-	2.8% pt-year	-	3.6% pt-year	2.6 year
Garadah et al, 2011 [13]	0.79%	-	-	-	-	-	-	-	-
Khan et al, 2014 [15]	18.2% AMI	-	-	-	-	13.6%	-	-	-
Rehman et al, 2017 [18]	14.2% AMI	-	-	-	-	12.2%	-	-	-
Sadeghi et al, 2015 [20]	9.0% Stroke	-	-	-	-	-	-	-	-
Non-AF registries									
Ajlan et al, 2018 [26]	6.7% AHF	9.1%	23.2%	27.4%	27.8%	2.0%	-	1.1%	-
Hersi et al, 2012 [27]	14.7% ACS	18.4%	22.1%	-	-	2.8%	-	1.4%	-
Cardiology and Cardiovascular Surgery Database									
Salam et al, 2012 [30]	3.6% 2007 to 2010	-	-	-	-	-	-	-	-
Salam et al, 2013 [46]	3.6% 2007 to 2010	-	-	-	-	1.1% 2007 to 2010	-	-	-
Salam et al,	4.8% / 2007 to 2010	-	-	-	-	1.4% / 2007 to 2010	-	-	-

First author	Mortality					CVA or TIA	Hospitalization	Major bleeding	F/U period
	In-hospital	30-day	1-year	2-year	3-year				
2013 [47] **ME vs. SA**	1.2%					0.6%			
Salam et al, 2013 [48]	20.3% AMI	-	-	-	-	1.8%	-	-	-
Salam et al, 2013 [49]	5.7%	-	-	-	-	0.7%	19.6%	-	-
Salam et al, 2014 [50] **Palpitation vs. none**	1.1% / 6.6%	-	-	-	-	0% / 0.8%	-	-	-
Salim et al, 2018 [51] **CKD vs. none**	11.7% CKD / 4.0%	-	-	-	-	2.3% / 0.3%	-	-	-
AF registries									
Gulf SAFE registry									
Domek et al, 2020 [53] **DM vs. none**	-	-	14.4% / 9.6%	-	-	3.0% / 3.1%	27.1%□ / 19.5%	6.6% / 7.8%	1 year
Domek et al, 2020 [54] **Compliant vs. none (DM pts)**	-	-	5.8% / 15.9%	-	-	-	-	-	1 year
Gumprecht et al, 2020 [55] **Compliant vs. none**	-	-	7.3% / 13.1%	-	-	-	-	-	1 year
Miyazawa et al, 2019 [57] **Stroke vs. none**	-	-	-	-	-	6.3% / 2.4%	-	1.4% / 2.0%	1 year

First author	Mortality					CVA or TIA	Hospitalization	Major bleeding	F/U period
	In-hospital	30-day	1-year	2-year	3-year				
Shehab et al, 2017 [58]	-	-	15.0%	-	-	6.4%	-	1.7%	1 year
Zubaid et al, 2015 [59] **Any ED admission vs. AF ED admission**	-	-	15.3% / 4.2%	-	-	4.2% / 2.2%	21.7%□ / 17.5%	1.2% / 0.2%	1 year
South Asian countries									
Single-centre studies									
Dhungel et al, 2017 [35] **NVAF vs. valvular**	-	-	-	-	-	17.2%° / 23.1%°	-	2.6%° / 2.0%°	-
Srisilpa et al, 2020 [36]	26.8% Stroke	-	-	-	-	-	-	-	3 month
Multi-centre studies									
Apiyasawat et al, 2015 (Ref New29)	1.6%	-	18.1%	-	31.8%	-	-	-	6 year
Non-AF registries									
Negi et al, 2018 [39] **AF vs. none**	0.75%▪ / 0.19%▪	- RHD	-	-	-	6.7% / 4.1%	-	-	-
AF registries									
Charantharayil et al, 2019 [40]	-	-	12.9%*	-	-	-	16.9%#	-	1 year
Krittayaphong et al, 2020 [60]	-	-	-	7.8%▪	-	3.0%	-	4.4%	25.7 month

First author	Mortality					CVA or TIA	Hospitalization	Major bleeding	F/U period
	In-hospital	30-day	1-year	2-year	3-year				
Sawhney et al, 2018 [43]	-	-	7.68[!]	-	-	0.85[!]	-	0.31[!]	
Vora et al, 2017 [44]	-	-	6.5%[&]	-	-	1.0%[§]	8.0%[$]	0.85% (2.7%; any)	1 year

◊ In patients with high risk of bleeding
Δ Included inappropriate NOACs dosing group (9.9%) and appropriate dosing group (3.1%)
● Included inappropriate dosing group (11.7%) and appropriate dosing group (6.0%)
□ Includes HF and AF admission rates at one-year follow up
○ Reported as clinical presentation upon admission
* Causes of mortality: cardiac 9.7%, stroke 1.8%, others 1.4%
# Causes of hospitalization: stroke/TIA 1.9%, acute coronary syndrome 5.9%, arrythmia 5.1%, heart failure 2.2%, bleeding (any) 1.6%
▪ Time of mortality not specified
! Events are per 100 person-years
& Causes of mortality: heart failure 35%, myocardial infarction 14%, sudden cardiac death 12%, stroke 4.0%, non-cardiac 12.0%
$ Causes of hospitalization: stroke 13.0%, heart failure 10.0%, angina needs revascularization 13.0%
§ 16 patients represent 1.0% of patients; 15 out 16 patients were on OAC with mean INR of 1.85 (8 with ischemic stroke, 6 with haemorrhagic stroke, 2 undetermined type. 4 of them died)

CKD; chronic kidney disease, CVA; cerebrovascular, DM; diabetes mellitus, F/U; follow-up, NVAF; non-valvular atrial fibrillation, pt; patient, TIA; transient ischemic attack

6. List Of Relevant Publications

Other relevant publications by candidate not included to thesis are:

I. **Salam AM**, Ahmed MB, Sulaiman K, Singh R, Alhashemi M, Carr AS, Alsheikh-Ali AA, AlHabib KF, Al-Zakwani I, Panduranga P, Asaad N, Shehab A, AlMahmeed W, Al Suwaidi J. Clinical presentation and outcomes of peripartum cardiomyopathy in the Middle East: a cohort from seven Arab countries. ESC Heart Fail. 2020 Sep 23;7(6):4134–8. doi: 10.1002/ehf2.13030. Epub ahead of print. PMID: 32964700; PMCID: PMC7754996.

II. **Salam AM**, Ertekin E, van Hagen IM, Al Suwaidi J, Ruys TPE, Johnson MR, Gumbiene L, Frogoudaki AA, Sorour KA, Iserin L, Ladouceur M, van Oppen ACC, Hall R, Roos-Hesselink JW. Atrial Fibrillation or Flutter During Pregnancy in Patients With Structural Heart Disease: Data From the ROPAC (Registry on Pregnancy and Cardiac Disease). JACC Clin Electrophysiol. 2015 Aug;1(4):284-292. doi: 10.1016/j.jacep.2015.04.013. Epub 2015 Jun 22. PMID: 29759316.

III. **Salam AM**. Dronedarone in atrial fibrillation: the aftermath of the PALLAS trial. Expert Rev Cardiovasc Ther. 2012 Nov;10(11):1345-9. doi: 10.1586/erc.12.118. PMID: 23244355.

IV. Hassan OF, Al Suwaidi J, **Salam AM**. Anti-Arrhythmic Agents in the Treatment of Atrial Fibrillation. J Atr Fibrillation. 2013 Jun 30;6(1):864. doi: 10.4022/jafib.864. PMID: 28496859; PMCID: PMC5153068.

V. **Salam AM**, Sulaiman K, Alsheikh-Ali AA, Singh R, Asaad N, Al-Qahtani A, Salim I, AlHabib KF, Al-Zakwani I, Al-Jarallah M, AlMahmeed W, Bulbanat B, Ridha M, Bazargani N, Amin H, Al-Motarreb A, Al Faleh H, Albackr H, Panduranga P, Shehab A, Al Suwaidi J. Acute heart failure presentations and outcomes during the fasting month of Ramadan: an observational report from seven Middle Eastern countries. Curr Med Res Opin. 2018 Feb;34(2):237-245. doi: 10.1080/03007995.2017.1376629. Epub 2017 Oct 3. PMID: 28871820.

VI. **Salam AM**, AlBinali HA, Singh R, Al-Qahtani A, Asaad N, Al Suwaidi J. Gender Variations in In-Hospital Mortality in Patients Hospitalized With Dizziness: A Retrospective Study.

Angiology. 2017 Nov;68(10):914-918. doi: 10.1177/0003319717703225. Epub 2017 Apr 7. PMID: 28387126.

VII. Shehab A, AlHabib KF, Bhagavathula AS, Hersi A, Alfaleh H, Alshamiri MQ, Ullah A, Sulaiman K, Almahmeed W, Al Suwaidi J, Alsheikh-Ali AA, Amin H, Al Jarallah M, **Salam AM**. Clinical Presentation, Quality of Care, Risk Factors and Outcomes in Women with Acute ST-Elevation Myocardial Infarction (STEMI): An Observational Report from Six Middle Eastern Countries. Curr Vasc Pharmacol. 2019;17(4):388-395. doi: 10.2174/1570161116666180315104820. PMID: 29542414.

VIII. Ertekin E, van Hagen IM, **Salam AM**, Ruys TP, Johnson MR, Popelova J, Parsonage WA, Ashour Z, Shotan A, Oliver JM, Veldtman GR, Hall R, Roos-Hesselink JW. Ventricular tachyarrhythmia during pregnancy in women with heart disease: Data from the ROPAC, a registry from the European Society of Cardiology. Int J Cardiol. 2016 Oct 1;220:131-6. doi: 10.1016/j.ijcard.2016.06.061. Epub 2016 Jun 23. Erratum in: Int J Cardiol. 2017 Apr 1;232:348. PMID: 27376569.

IX. Salim I, Al Suwaidi J, Ghadban W, Alkilani H, **Salam AM**. Impact of religious Ramadan fasting on cardiovascular disease: a systematic review of the literature. Curr Med Res Opin. 2013 Apr;29(4):343-54. doi: 10.1185/03007995.2013.774270. Epub 2013 Feb 18. PMID: 23391328.

X. Salim I, Al Suwaidi J, Ghadban W, **Salam AM**. Anticoagulation in atrial fibrillation and co-existent chronic kidney disease: efficacy versus safety. Expert Opin Drug Saf. 2013 Jan;12(1):53-63. doi: 10.1517/14740338.2013.732569. Epub 2012 Oct 24. PMID: 23095103.

XI. **Salam AM**. Managing atrial fibrillation in older people: a comparison of two treatment strategies. J Am Geriatr Soc. 2003 Dec;51(12):1806-7. doi: 10.1046/j.1532-5415.2003.51568.x. PMID: 14687362.

XII. **Salam AM**. Rate control versus rhythm control for the management of atrial fibrillation: the verdict of the AFFIRM trial. Expert Opin Investig Drugs. 2003 Jul;12(7):1231-7. doi: 10.1517/13543784.12.7.1231. PMID: 12831357.