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Prognostic impact of atrial fibrillation on clinical outcomes of acute coronary syndromes, heart failure and chronic kidney disease

Nileshkumar J Patel, Aashay Patel, Kanishk Agnihotri, Dhaval Pau, Samir Patel, Badal Thakkar, Nikhil Nalluri, Deepak Asti, Ritesh Kanotra, Sabeeda Kadavath, Shilpkumar Arora, Nilay Patel, Achint Patel, Azfar Sheikh, Neil Patel, Apurva O Badheka, Abhishek Deshmukh, Hakan Paydak, Juan Viles-Gonzalez

Nileshkumar J Patel, Dhaval Pau, Nikhil Nalluri, Deepak Asti, Ritesh Kanotra, Azfar Sheikh, Cardiovascular Division, Staten Island University Hospital, Staten Island, NY 10305, United States

Aashay Patel, Cardiovascular Division, Lankenau Institute of Medical Research, Wynnewood, PA 19096, United States

Kanishk Agnihotri, Nilay Patel, Cardiovascular Division, Saint Peters University Hospital, New Brunswick, NJ 08901, United States

Samir Patel, Cardiovascular Division, Western Reserve Health Education, Yougstown, OH 44504, United States

Badal Thakkar, Cardiovascular Division, Tulane University School of Public Health and Tropical Medicine, New Orleans, LA 70112, United States

Sabeeda Kadavath, Cardiovascular Division, Lincoln Medical and Mental Health Center, Bronx, NY 10451, United States

Shilpkumar Arora, Cardiovascular Division, St. Lukes Roosevelt Hospital, New York, NY 10025, United States

Achint Patel, Neil Patel, Cardiovascular Division, Icahn School of Medicine at Mount Sinai, New York, NY 10029, United States

Apurva O Badheka, Cardiovascular Division, Yale School of Medicine, New Haven, CT 06519, United States

Abhishek Deshmukh, Cardiovascular Division, Mayo Clinic, Rochester, MN 55905, United States

Hakan Paydak, Cardiovascular Division, University of Arkansas for Medical Sciences, Little Rock, AR 72205, United States

Juan Viles-Gonzalez, Cardiovascular Division, University of Miami Miller School of Medicine, Miami, FL 33136, United States

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Correspondence to: Nileshkumar J Patel, MD, Cardiovascular Division, Staten Island University Hospital, 475 Seaview Avenue, Staten Island, NY 10305, United States. dr.nilesh.j.patel@gmail.com
Telephone: +1-201-7449111
Fax: +1-610-3941787

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Abstract

Atrial fibrillation (AF) is the most common type of sustained arrhythmia, which is now on course to reach

epidemic proportions in the elderly population. AF is a commonly encountered comorbidity in patients with cardiac and major non-cardiac diseases. Morbidity and mortality associated with AF makes it a major healthcare burden. The objective of our article is to determine the prognostic impact of AF on acute coronary syndromes, heart failure and chronic kidney disease. Multiple studies have been conducted to determine if AF has an independent role in the overall mortality of such patients. Our review suggests that AF has an independent adverse prognostic impact on the clinical outcomes of acute coronary syndromes, heart failure and chronic kidney disease.

Key words: Atrial fibrillation; Heart failure; Chronic kidney disease; Acute coronary syndromes; Prognostic impact

Core tip: Atrial fibrillation (AF), the most common type of arrhythmia, is on course to reach epidemic proportions in the elderly. AF is a commonly encountered comorbidity in patients with acute coronary syndromes, heart failure and chronic kidney disease. Multiple studies have been conducted to determine if AF has an independent role in the overall mortality of such patients. Our review suggests that atrial fibrillation has an independent adverse prognostic impact on the clinical outcomes of acute coronary syndromes, heart failure and chronic kidney disease.

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INTRODUCTION

Atrial fibrillation (AF) is a commonly encountered arrhythmia in clinical practice[1] with an increased prevalence being reported with advanced age[2]. It is estimated that more than 8 million patients over the age of 80 will be affected by the year 2050[1,3]. Consequently, the associated healthcare expenses are also rising and have reached an all-time high of 16 to 26 billion dollars annually[4]. The major contributors to the burgeoning healthcare costs of AF include outpatient care and testing which accounted for nearly $1.5 billion of the total costs, prescription drugs that cost an approximate of $235 million, and also high costs associated with inpatient interventional procedures[4-6].

With a rising prevalence and economic burden, there is concern in the medical community regarding the temporal effect of cardiovascular conditions including atrial fibrillation on the clinical outcomes of associated comorbidities. In addition to its deleterious health consequences, cardiovascular disease is the number one cause of death in the United States and globally[7]. It is important to understand the role of other comorbidities in cardiovascular disease to prevent and reduce this mortality. In this article we focus on atrial fibrillation and commonly associated comorbidities. Atrial fibrillation is commonly encountered in the setting of acute coronary syndromes, heart failure and chronic kidney disease. The purpose of this article is to review the prognostic impact of atrial fibrillation on these comorbid conditions.

ACUTE CORONARY SYNDROMES

Acute coronary syndrome (ACS) is commonly associated with concomitant or incident AF. Most of the studies conducted have noted that the incidence of AF in ACS ranges from 2.3% to 23%[8]. Multiple factors explain this wide range of variation. The Cooperative Cardiovascular Project by Rathore *et al*[9] reported a higher incidence of AF in ACS patients, as the subjects were primarily elderly patients. Eldar *et al*[10] reported a lower incidence as they studied only paroxysmal AF. Some randomized controlled trials like TRACE and OPTIMAAL which studied the efficacy of angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) in acute myocardial infarction (AMI) have also reported lower incidences; the efficacy of these drugs in preventing atrial fibrillation had however been proven in earlier studies[11,12].

Broadly there has been a downward trend in the incidence of AF in AMI in studies done over time. This can be explained possibly by more widespread use of thrombolytic therapy and percutaneous coronary interventions (PCI) over the years. Advanced age, tachycardia at the time of admission, and advanced stage of heart failure were found to be the major clinical predictors of atrial fibrillation in patients with AMI[9,13,14].

Early studies done to assess the independent prognostic impact of atrial fibrillation on ACS outcomes were found to have contrasting results. A number of studies after multivariate analyses found atrial fibrillation to have no independent impact and concluded that it was more the coexisting comorbidities that contributed to the mortality[10,14-19]. However, a greater number of studies have reported that atrial fibrillation in the setting of AMI, results in a worse prognostic outcome[9,11-13,19-22].

However, two major meta-analyses done by Jabre *et al*[23] and Angeli *et al*[24] proved conclusively the independent impact atrial fibrillation had on AMI. In the analysis of 43 studies by Jabre *et al*[23] where 278854 patients were studied, it was observed that AF was associated with a 40% increase in risk mortality as compared to patients with normal sinus rhythm. While the impact of atrial fibrillation on both in hospital

mortality and long term mortality was noted, the timing of atrial fibrillation development, *i.e.*, new onset or pre-existing AF was not a contributor to the poor outcome as per this meta-analysis. Angeli *et al*[24], on the other hand, found that new onset atrial fibrillation had worse outcomes with an 87% higher risk compared to pre-existing atrial fibrillation. The study however only assessed in hospital mortality and not long-term outcomes.

Atrial fibrillation leads to a number of hemodynamic effects such as loss of atrial contraction, rapid ventricular rates, loss of atrio-ventricular synchrony and an irregular RR interval. All of these factors lead to a decreased cardiac output, which in turn explain the higher mortality rates[25,26].

Many mechanisms have been proposed to explain how AF is commonly encountered in the setting of ACS. Although many theories exist, the pathophysiological mechanism of the onset of AF after ACS is still not clearly understood. Conclusions drawn from experimental models and clinical investigations have shown different factors accounting for new-onset AF in ACS; it can be explained either by myocardial infarction causing atrial ischemia or atrial stretch[27]. Role of inflammation, autonomic nervous system activity, BNP and other hormone activation cannot be excluded as possible mechanisms for AF development in this patient subset[28,29]. Thus, proper understanding of the role of new onset AF complicating ACS can provide us with a new approach in formulating therapeutic guidelines.

Consensus has been reached on the independent role of AF on mortality in ACS. Treatment targeting the pathophysiological mechanism of AF development in ACS remains an area that needs to be explored. It therefore remains imperative to develop strategies to prevent AF onset and initiate aggressive treatment in case of a new onset AF in ACS.

HEART FAILURE

Heart failure (HF) and AF are closely linked cardiovascular diseases that often coexist and share a complex pathophysiological relationship. Both have continuously increasing prevalence, and the presence of AF in HF patients has been reported as being anywhere between 10% and 50%[30]. The difference in coexistence of this two-disease condition can be attributed to the different study settings, study design, severity of heart failure and other factors[30,31]. The prevalence of AF correlates directly with the severity of HF, as about 5% of patients with New York Heart Association (NYHA) class Ⅰ HF have AF and this prevalence increases to about 50% in NYHA class IV HF[32,33]. Regardless of the study design, a few factors like hypertension, prior history of ACS, diabetes, and obesity were commonly observed to be associated with an increasing prevalence of AF and HF.

Recent large heart failure trials have demonstrated the adverse prognostic influence of AF on HF[34]. A study conducted by Dries *et al*[35], in which data was obtained from SOLVD trial, showed AF was associated with an increased risk of all cause mortality in patients with symptomatic and asymptomatic left ventricular systolic dysfunction[35]. On the other hand, the COMET trial analysis by Swedberg *et al*[36] showed AF did increase mortality risk and HF hospitalizations but it was not identified as an independent risk factor for mortality when adjustment for other prognostic indicators was made[36].

AF also increases re-hospitalization rates, hospital stays, and has an overall adverse prognosis in HF patients that is very clearly evident in many studies. Mountantonakis *et al*[37] analyzed data obtained from 99810 patients enrolled in the Get with the guidelines - Heart failure Registry and concluded that AF independently was associated with adverse hospital outcomes and a longer length of in-hospital stay. Mentz *et al*[38] showed presence of AF on initial electrocardiogram in patients hospitalized with HF was associated with higher readmission, higher mortality and lower use of evidence-based therapies.

Corell *et al*[39] proved an adverse prognostic impact of AF in HF patients. Olsson *et al*[40] reviewed results from Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) program and showed that AF is associated with an increased risk of poor cardiovascular outcomes. In the meta-analysis by Mamas *et al*[41] which included 16 studies involving 53969 patients; the conclusion was that irrespective of left ventricular systolic function, AF has an overall adverse prognosis in HF patients.

Pathophysiological changes that explain the increased prevalence of AF in HF patients are not very well understood. It is difficult to ascertain in most cases if HF leads to AF or changes due to AF leads to worsening of the underlying HF. Studies have different conclusions on the cause - effect process but there is a general agreement about the vicious cycle of deterioration when both conditions co-exist. According to one thought process, HF results in specific electrophysiological changes in the atrium like prolonging the atrial refractory period or increasing heterogeneity of repolarization that leads to the development of AF[42]. On the other hand, HF also plays a part in concurrent worsening of AF through mechanical and hemodynamic changes. Atrial tissue stretching occurs as a result of the increased pressure and volume in HF patients, which in turn triggers AF by increasing automaticity and altering atrial repolarization[43]. Activation of the renin-angiotensin system secondary to HF and other neurohormonal changes also promotes the development of AF[43]. Further studies need to be conducted to understand the impact AF has on HF, especially in regards to the dynamic pathophysiological interplay and therapy should be aimed at correcting the predisposing factors.

Although beyond the scope of this article, the op-

timal management approach of AF in HF remains unclear. Pharmacological therapy remains the mainstay of choice in AF, and includes rate control and rhythm control. A recent meta-analysis involving 2486 patients suggested no significant difference in terms of mortality and thromboembolic events between both modes of pharmacological management. However, hospitalizations appear to be less frequent with rate control than with rhythm control[44]. Also there are data that suggest role of cardiac resynchronization therapy (CRT) in non-ischemic dilated cardiomyopathy and severe heart failure, which has favorable outcome on incidence of AF[45,46]. Further studies are warranted to determine the optimal management approach for AF in patients with HF.

CHRONIC KIDNEY DISEASE

It is a well-established fact that there is a high occurrence of cardiovascular disease in patients with chronic renal insufficiency. The overall prevalence of AF is higher among patients with end-stage renal disease (ESRD)[47]. Studies examining the prevalence of AF in cohorts pooled from the Dialysis Outcomes and Practice Patterns Study (DOPPS) and the United States Renal Data System (USRDS) estimated the occurrence of AF to range from 6% to 27% among patients with ESRD on dialysis[48-50]. This high rate of occurrence in ESRD patients is nearly two times higher than that reported in the general population[49]. Dissimilarity of the individual study pattern, study population, sample size, disease definition and diagnostic methods of AF can account for the difference between the prevalence of AF in this population.

Wetmore *et al*[50] and Wizemann *et al*[48] concluded that a significantly higher prevalence of AF exists in ESRD patients on dialysis. On the other hand, recent studies have found a higher incidence and prevalence of AF among patients with chronic kidney disease (CKD) who have not been started on dialysis, as is clearly evident in the ARIC study and CRIC study done by Alonso *et al*[51] and Soliman *et al*[52]. In the latter study by Soliman *et al*[52] where a multicenter cohort with a wide range of kidney function was studied, it was estimated that the prevalence of AF was at 18%.

Moreover, AF is an independent risk factor for ischemic stroke and death among patients with ESRD on dialysis[53]. A large cross sectional cohort study conducted by Winkelmayer *et al*[49], analyzed data from 1992 to 2006 for the prevalence of AF in hemodialysis patients from the United States Renal Data System (USRDS). According to this study, the prevalence of AF increased 3 fold from 3.5% in 1992 to 10.7% in 2006. A one-year mortality rate among patients with AF was twice that of those without AF and was as high as 72% after demographic variant adjustment was made.

Several mechanisms have been proposed to explain the increased risk of death in CKD patients with AF. Systemic inflammation could be responsible for the fibrotic changes seen in the kidney and myocardium and by could worsen cardiovascular outcomes such as heart failure, thromboembolic risk and stroke which in turn increases the risk of morbidity and mortality[35,54-57].

A large cohort study on adults with AF by Go *et al*[58] concluded that a lower level of GFR was associated with an increased risk of thromboembolism independent of the known AF risk factors. A higher rate of thromboembolic events was observed among individuals with a lower estimated GFR.

The cumulative effect of AF and CKD together has been shown to not only increase mortality but also the rate of cardiovascular events, as has been observed in two separate studies done by Nakagawa *et al*[59] in Japan and Genovesi *et al*[60] in Italy. From the findings of the study by Nakagawa *et al*[59], it was determined that a lower eGFR (< 60 mL/min per 1.73 m^2) with CHADS2 score > 2 was associated with a higher all-cause (12.9% *vs* 1.4% per year, $P < 0.001$) and cardiovascular (6.5% *vs* 0.2% per year, $P < 0.001$) mortalities compared to preserved eGFR (> 60 mL/min per 1.73 m^2) combined with CHADS2 score < 2. Also cardiovascular events, which include cardiac death, nonfatal myocardial infarction, or hospitalization for worsening of heart failure and ischemic stroke risk, were much higher in the same group (13.6% *vs* 1.5% per year, $P < 0.001$). The study concluded that a combined eGFR and CHADS2 score could be an independent powerful predictor of cardiovascular events and mortality in patients with nonvalvular AF[59].

Although there is a substantially increased risk of thromboembolism in patients with CKD and AF, there are no distinct guidelines to follow for thromboembolism prophylaxis in AF patients with CKD when compared to patients without CKD. Patients with severe renal impairment have been excluded from a vast majority of trials studying stroke prevention in AF, including trials that have formed the landmark for risk factor scoring schemes and guidelines. It therefore, poses a huge challenge to healthcare providers to treat this subset of patients. The available data suggests that the benefit from warfarin in terms of stroke reduction in CKD patients is not as clear as in the general population, and there is also an increased risk of bleeding complications[61].

One of the few studies that show a favorable outcome of anticoagulation for prevention of stroke in renal failure patients is the study by Hart *et al*[62]. Efficacy of adjusted-dose warfarin in prevention of stroke in atrial fibrillation patients with stage 3 CKD was demonstrated by this study. The study by Chan *et al*[63], a large retrospective cohort study of patients with AF on hemodialysis, suggests that warfarin use is associated with an increased risk for ischemic (HR = 1.81; 95%CI: 1.12-2.92) and hemorrhagic (HR = 2.22; 95%CI: 1.01-4.91) stroke. The data however is influenced by lack of appropriate monitoring and

difficulties in maintaining the international normalized ratio (INR) target[63].

Thus, it remains a dilemma to refer to the benefits of warfarin administration as has been determined by anticoagulation guidelines in the general population, to a group of people that have been actively excluded from clinical trials; the prediction rules for bleeding risk would be inaccurate and oversimplified and probably not suitable for clinical practice. In reality, there appears to be no large randomized controlled trials that evaluate the real risk *vs* benefit of full intensity anticoagulation including newer novel anticoagulants in patients with severe renal impairment. Information about management is limited and in the future there might be an opportunity to look into these patients and form risk stratification guidelines that can be followed.

LIMITATIONS

Although we have searched a wide range of appropriate literature from online data sources for our article, sometimes such studies are potentially susceptible to vary in conclusion due to different populations, settings, interventions, or outcome measures. All the studies we included have different limitations. Despite the limitations, the present article has important strengths, including a real-world large sample size from different studies and the absence of selection bias associated with clinical trials.

CONCLUSION

In conclusion, atrial fibrillation is a commonly encountered arrhythmia in clinical practice that has a rising prevalence and significant adverse prognostic implications on other comorbidities. In this article we concluded that AF, with its rising prevalence increases the economic burden on healthcare, and has an independent adverse prognostic impact on comorbidities like ACS, HF and CKD. A thorough understanding of AF prevalence and its pathophysiology, including the role of genetics, can serve as a potential biomarker for the prevention and treatment of AF[64,65]. Along with it, factors associated with AF and its increased association with other comorbidities, outcomes of these comorbidities in the setting of AF, prospective data and appropriate guidelines are needed to define more precisely how to treat these patients. Individual risk stratification may represent the best possible approach and provide opportunities for improvement in the future. Further studies need to be conducted to determine risk stratification for decision making and to develop an optimal management approach.

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