Incidence and Prevalence of Atrial Fibrillation (AF) in End Stage Renal Disease (ESRD) Patients

Venkataraman Palabindala^{1*}, Sohail Abdul Salim¹, Amaleswari Pamarthy¹, Bharat Malhotra¹ and Shradha Ahuja¹

University of Mississippi Medical Center, Division of Hospital Medicine, School of Medicine, USA

Article Information

Received date: Nov 21, 2016

Accepted date: Jan 02, 2017

Published date: Jan 06, 2017

*Corresponding author

Venkataraman Palabindala, University of Mississippi Medical Center, Division of Hospital Medicine, School of Medicine, 2500 N State St, Jackson, MS, 39216, USA, Email: palabindala@gmail.com

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Keywords AF; ESRD; PD; HD; Stroke; Mortality

Article DOI 10.36876/smjnt.1006

Abstract

End Stage Renal Disease (ESRD) patients have been found to exhibit high prevalence of Atrial Fibrillation (AF), which demonstrates the possibility of a relationship of causality between the two conditions. The increased risk of stroke and mortality among ESRD patients with AF has also prompted a desire to understand the exact linkages between these different conditions.

We conducted extensive reviews of relevant literature and established that indeed ESRD patients with AF exhibited higher risks for mortality and stroke occurrence compared to individuals with AF that did not suffer from ESRD. We also established that anticoagulation is regularly used as a form of therapeutic intervention with drugs such as warfarin, apixaban, and aspirin being some of the choice anticoagulants. The ARISTOTLE study found apixaban to be more effective than warfarin with a major bleeding rate of 2.13% annually compared to 3.09% respectively. The AVERROES trial found that warfarin use made it harder to maintain INR values compared to apixaban.

This presence, severity, and duration of AF in ESRD patients was also found to correlate with structural abnormalities of the heart that significantly increased the risk for ischemic and hemorrhagic strokes as well as mortality. This risk of stroke was found to be higher in CKD patients compared to the general population. Age, diabetes, hyperlipidemia, and gout were also confirmed as core factors influencing the development of AF in ESRD patients, as well as risk factors for stroke occurrence and mortality. High blood pressure and anticoagulation complications were further identified as causative factors for mortality among ESRD patients with AF.

AF incidence is more prevalent among ESRD patients compared to the general population. This incidence and prevalence is also associated with more significant risk of stroke and mortality among said ESRD patients compared to the general population. However, more studies and trials need to be conducted on the prevalence of AF in the general population to fully understand the linkages between AF and ESRD.

Introduction

Chronic Kidney Disease (CKD) is considered one of the most debilitating illnesses that humanity can endure. Its negative prognosis does little to inspire confidence among the sick, seeing as the only two possible solutions are a kidney transplant or periodical dialysis. In addition to this, the widespread prevalence of Atrial Fibrillation (AF) among patients in the latter stages of CKD has drawn significant attention to the importance of understanding the relationships, if any, that exist between AF and the latter stages of CKD (End Stage Renal Disease, commonly referred to as ESRD). This paper seeks to understand the existing relationship between ESRD and AF, as well as the incidence and prevalence of AF in ESRD patients. This paper hopes to show that the prevalence and incidence of AF in ESRD patients is higher than in the general population, and that it is associated with an increased risk of stroke and mortality.

AF in ESRD Patients

Linkages between AF and ESRD

Atrial Fibrillation has been found to be a leading condition in ESRD patients, and one that has particularly had significant contribution to the detrimental health that many ESRD patients suffer [1]. As a comorbidity, AF has been a leading cause of death among ESRD patients, and especially so through its ability to cause stroke and eventual death. In the vast majority of patients those suffer from ESRD, the presence of Chronic Kidney Disease (CKD) has also been established, causing many of these patients to rely heavily on dialysis as a result of their kidney failure [2]. It is worth noting that in the limited amount of literature that attempts to understand the links between AF, ESRD, and mortality among CKD patients, there have been some strong similarities [3]. First, almost all patients suffering from CKD who had managed to reach the end stages of the disease, AF was prevalent [4], which greatly interfered with the ability of the heart to perform its normal functions as required [5]. Secondly, the literature has also established that a significant percentage of individuals

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ISSN: 2573-3613

suffering from ESRD also suffered coagulation problems, and as a result, were forced to take anticoagulant medications, with warfarin, dabigatran apixaban, and rivaroxaban being common prescriptions [6]. These medications were oral in nature. Thirdly, the literature also established that patients suffering from AF were five times more likely to suffer ischemic strokes compared to individuals that did not suffer from AF. However, this data seemed to be hinged on the fact that all patients examined in this respect were ESRD patients.

Stroke Probability and AF

Nonetheless, the probability of suffering from strokes among ESRD patients, and particularly in those patients that also suffered from AF was five times higher than it was in patients with ESRD, but without AF [3]. This complexity of data shed very little light on the probability of ischemic strokes occurring among the general population that neither suffered from ESRD nor AF. The complexity of AF conditions was also considered in the literature examined, and it was established that in order to ascertain the exact linkages between AF and ESRD in patients, the studies had to be adjusted to accommodate from demographic factors, blood pressure, the modality of dialysis applied to ESRD patients (whether peritoneal or hemodialysis) [7], comorbidities within said patients, as well as the various cardio-protective medications that patients were taking [1]. The literature establishes that indeed these factors play a significant role in understanding AF and ESRD, and the linkages that they share [3]. Of particular regard were factors such as age, the modality of dialysis used, and blood pressure [5], which greatly impacted the likelihood of mortality among ESRD patients suffering from AF as well.

Anticoagulation Agents and AF

The efficacy of anticoagulation as a therapeutic intervention in ESRD and AF patients draws significant debate from various authors with differing views on the literature. The use of anti-coagulants and anti-platelet agents was critically discussed by many authors as a possible remedy to ischemic strokes associated to ESRD and AF in patients [8]. However, the research firmly establishes that the linkages between the use of anti-coagulant and anti-platelet agents does very little to prevent ischemic strokes, which essentially renders drugs such as warfarin inconsequential in the fight against AF and ESRD related ischemic strokes [9]. This is in spite of the fact that some research had firmly suggested warfarin was effective in preventing ischemic strokes among ESRD patients who also suffered from AF [10]. However, the studies investigating the use of warfarin as a possible remedy failed to account for comorbidities, other medical conditions, demographics, and the dialysis modalities employed in the sample populations [11], thus casting doubts on the validity of the studies.

Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) Trial included patients with CrCl<30 ml/min and excluded those with CrCl<25 ml/min and showed that the rate of major bleeding was 2.13% per year with apixaban versus 3.09% per year with warfarin. Extracranial hemorrhage and death within 30 days was lower with apixaban than warfarin and at same time ischemic stroke was less likely with apixaban than aspirin without increased risk of bleeding as shown in AVERROES Trial (Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation). In CKD on Dialysis patients there is

variable warfarin responsiveness with extreme and rapid volume changes due to redistribution of body fluids. Also advanced CKD patients commonly have vitamin K deficiency and maintaining therapeutic INR might be a challenge. To date, randomized controlled trials assessing the efficacy and safety of warfarin in atrial fibrillation have systematically excluded patients with late stage CKD and those requiring RRT. As such, the entire evidence is based on observational studies [12]. A recent systematic review and meta-analysis of observational studies of warfarin and atrial fibrillation in CKD/ESRD included 13 publications from 11 cohorts. In patients with atrial fibrillation and ESRD, warfarin did not decrease the risk of stroke or death but was associated with a higher risk of major bleeding [13]. Warfarin is also associated with glomerular hemorrhage and anticoagulant associated nephropathy seen in CKD and may accelerate CKD progression. Calcific Uremic Arteriopathy is characterized by medial calcifications of arteries leading to painful, ulcerative skin lesions and is also associated with warfarin therapy. Matrix GLA protein is an inhibitor of calcification in the arterial wall whose activity is inhibited by warfarin [14].

Heart Conditions and AF

In addition to this, the roles of other heart diseases and left atrial dilation in facilitating AF have also been investigated. The studies firmly establish that in patients that have a long history of hemodialysis, left atrial dilation is highly probable, which inadvertently facilitates the onset of arrhythmia within patients suffering from ESRD [15]. However, there were no linkages of any sort established between both hypertension and diabetes and said arrhythmia. This factor has been identified as a determinant of mortality among a significant percentage of AF patients who also suffer from ESRD [3]. Due to this, there has been ongoing debate regarding the management of AF, and in particular among patients that also suffer from ESRD, seeing as they are considered a significant at-risk population [15]. Uremia is associated with structural abnormalities of the heart, including hypertrophy of cardiomyocytes, interstitial fibrosis, and vascular changes (thickened arteriolar walls) and the extent of fibrosis is significantly correlated with AF presence, severity, and duration. Chronic inflammation in the atrial myocardium is likely to play an important role in this process [16]. With Peritoneal Dialysis there is better preservation of renal function, more hemodynamic stability, higher hemoglobin concentration with less left ventricular hypertrophy and improved survival, thus one would assume that there is lesser risk of incident atrial fibrillation in PD than HD [17]. The ability of AF and ESRD to facilitate ischemic strokes, and in particular cardioembolic strokes, is unquestionable, and more so in certain patient groups. For this reason, increased management of AF among ESRD patients continues to be recommended as a solution to reducing strokes and mortalities that result from AF and ESRD in CKD patients.

Risk of Stroke and Mortality

Stroke Probability and ESRD Patients

While AF has been found to be highly likely among ESRD patients, the possibility of said patients suffering from stroke continues to solicit much discussion and debate due to the limited scope of data, from which researchers have to dig for relationships. This has also generated much interest due to the differences that exist between

stroke likelihood in ESRD patients with AF, and those that do not (“Independent predictors of stroke in patients with atrial fibrillation: A systematic review”, 2007) [18]. There have also been spirited efforts to understand the role that age plays in the probability of stroke in ESRD patients. While age has been consistently observed as a factor facilitating ESRD and stroke from the perspective of the aging, Hung et al. observed that age can also be observed from the perspective of the young. In their study, they firmly establish that young males aged between 25 and 44 were at great risk of developing ESRD later in their lives if they had already suffered a stroke [19]. This study essentially established that the relationship between ESRD and stroke was not only based on the fact that ESRD patients were likely to suffer strokes, but also that young stroke patients had significant chances of suffering from ESRD in their later years [9]. This finding demands a more in-depth understanding of the relationship between ESRD and stroke, seeing as it now appears that either can be a causative factor for the other. This relationship can be likened to a chemical redox reaction, where in this case, ESRD can cause strokes and vice versa. Hung et al. also established that renal functionality in stroke patients was a viable topic for further research, to facilitate a proper understanding of this relationship [19].

In a different study, Wang et al. established that in ESRD patients, the modality of dialysis that patients were subjected to have significant ramifications of the probability of stroke [20]. They concluded that patients being subjected to dialysis modality of Peritoneal nature (PD) exhibited a lesser likelihood of developing strokes of the hemorrhagic kind compared to patients undergoing Hemodialysis (HD) [7,9]. To control their study, they compared this sample's results to those of the general population. The comparisons firmly asserted that both HD and PD patients were more likely to develop ischemic and hemorrhagic strokes compared to the general population [9]. However, after adjusting their study to facilitate all comorbidities and confounders, they also established that differences in the likelihood of both PD and HD patients suffering ischemic strokes were insignificant. As such, according to Drew & Sarnak the relationship between hemorrhagic stroke and ESRD demanded further insights to ascertain the factors that facilitate increased likelihood of HD patients suffering from hemorrhagic strokes [9]. In their study, the sample populations under study were all undergoing long-term dialysis maintenance.

The Risk of Ischemic stroke is higher with CKD patients on dialysis than the general population due to multiple coexisting comorbidities. CHA2DS2-VASc score was derived from non-renal patients and may not be valid in advanced CKD or CKD on dialysis. ATRIA risk score (anemia, severe renal diseases, age ≥ 75 years, prior bleeding and hypertension) derived from 9186 subjects and included patients with GFR < 30 mL/min. Patients with a GFR < 30 mL/min exhibited a significantly (4.3-fold) increased risk of major hemorrhage.

Core Considerations in Assessing Stroke Probability in ESRD Patients

One of the most important considerations for assessing stroke probability is age. In many of the studies conducted regarding ESRD, AF and stroke probabilities, the majority of participants were ESRD patients, many of whom were well past the age of 50, with the majority being around 60 years old. One of the commonalities drawn from the various samples was the early onset of CKD, which had gradually

taken its toll on the patients, with almost all of them suffering from ESRD [6]. However, several studies have also been conducted on the risk of ESRD among young populations, and the results showed very little differences between the old and the young ESRD patients in terms of incidence, prevalence, and the probability of stroke and mortality. This enigmatic finding can be attributed to the two-way relationship that ESRD and stroke probability share. Consequently, it is fundamental that age as a factor is always considered is assessing stroke probability in ESRD patients [21]. It allows researchers to identify common factors that facilitate either ESRD or stroke, and identify how they are related to age. In this way concrete deductions on the relationship between ESRD, AF, stroke, and age can be determined.

Comorbidities are also significant considerations in the attempt to understand stroke probability and its relationship to AF and ESRD. In a significant number of the studies that were assessed, adjustment was made to the findings to accommodate for any comorbidities that may have resulted in stroke or mortality that were not related to AF and ESRD. One of the common factors adjusted for was diabetes [22]. In a large population of the samples across different studies, ESRD, AF and stroke patients also had diabetes [23]. In the vast majority, however, the onset of diabetes had been before the patients suffered ESRD, but not always before they suffered from AF. Hyperlipidemia and gout were also identified as some of the core comorbidities within ESRD and AF patients [22]. Within populations that were below 50 years of age, these comorbidities were linked with a high likelihood of suffering ischemic or hemorrhagic strokes [22].

Mortality: Causes and Likelihood in ESRD Patients

While there may exist a host of mortality causes in ESRD patients, the leading one remains kidney failure. For the vast majority of patients suffering from AF and ESRD, eventual kidney failure played a core role in the direction that their healthcare took [5]. Seeing as kidney transplants are often complicated by the need to find a proper match, many patients resort to dialysis as a form of managing their ESRD [3]. The engagement of many ESRD patients in long-term dialysis has been found to significantly contribute towards the onset of stroke, as well as the development of treatment complications that resulted in mortality. This ascertains the role that kidney failure plays in ESRD patients with AF insofar as mortality is the subject matter of discussion.

In addition to kidney failure, other comorbidities such as diabetes, hyperlipidemia, gout, and high blood pressure were also identified as causative factors of mortality among AF and ESRD patients. Moreover, complications associated with thromboprophylaxis and anticoagulation and antiplatelet therapy [8] also resulted in mortality among ESRD patients also suffering from AF. This vast spread of comorbidities significantly impairs the ability for researchers to draw conclusive assertions regarding the impact of AF, on its own, on ESRD patients [24]. The fact that medication also has to be factored into the assessment further complicates this process. This is essentially because many AF and ESRD patients are on long-term medication, most of which are aimed at managing the prevalent comorbidities that they are exposed to. As such, it becomes difficult for research to establish finite linkages between AF, ESRD, and mortality, without having to include comorbidities and medications within the same assessment [5]. In terms of mortality likelihood, the small data pool

to which researchers are disposed presents very minimal information on mortality among ESRD patients that also suffer from AF, and the causative factors of said mortality [5]. This vagueness and absence of sufficient data makes it virtually impossible to draw conclusive positions regarding the likelihood of mortality among ESRD patients with AF. This area should be greatly considered for further research, which would allow linkages between ESRD, AF, and mortality (devoid of all other comorbidities) to be established.

Comparisons of AF Prevalence between ESRD Patients and the General Population

Causative Factors

One of the leading causative factors of AF prevalence among ESRD patients is the kidney failure from which ESRD patients suffer. This kidney failure has been established as having significant impact on overall health, the worsening of comorbidities and the onset of AF among ESRD patients [21]. In addition to said kidney failure, other comorbidities such as high blood pressure have been found to greatly facilitate the onset of AF among ESRD patients, which, in turn, facilitates stroke development and eventual mortality among patients.

AF is found to have greater prevalence in ESRD patients, and especially so when the general population is used as a measure. This subsequently results in greater rates of AF-associated comorbidities, as well as AF-associated mortality among ESRD patients [25]. Within the general population, the development of AF is in itself significantly rare, and the absence of sufficient data on the general population and ESRD prevalence limits the scope from which conclusions can be drawn.

Impact on Stroke Probability and Mortality Rates

While it has been established that stroke probability in AF patients that suffer from ESRD is considerably higher than in patients within the general population that do not suffer from ESRD, there still needs to be more research into the matter [24]. The lack of clearly defined correlations and causative factors between stroke probability and AF in the general population calls for more in-depth research. Consequently, in order to critically understand stroke probability in AF patients, considerable data on the general population must be collected and compared with the existent data on ESRD patients [26]. In this way, accurate comparisons can be drawn regarding stroke probability and AF prevalence in ESRD patients and the general population. This insight will also help to shed light on mortality.

Conclusion

The relationship between AF and ESRD has been found to be cyclic in nature, with either one being very possible of causing the other. Among ESRD patients, however, the prevalence and incidence of AF has been found to be much higher than it is in the overall populace. This conclusion is based on the extensive data on AF in ESRD patients that allows for a proper analysis of prevalence compared to the less voluminous data available on AF incidence and prevalence in the general population. The occurrence of AF in ESRD patients has also been closely linked to increased stroke risk, both hemorrhagic and ischemic within ESRD patients. The limitations to extrapolating use of risk assessment scales for AF in ESRD and uncertainty of using

traditional versus novel anticoagulation have also been discussed. Within the general population with AF, insufficient data on stroke and mortality risk make it impossible to draw conclusions on prevalence and incidence with the population. However, this paper establishes that indeed prevalence and incidence of AF in ESRD patients is much more established than within the overall populace. The paper also finds that it is linked to higher mortality and stroke risks in ESRD patients when compared against the overall populace.

References

- Abbott K, Trespalacios F, Taylor A, Agodoa L. Atrial fibrillation in chronic dialysis patients in the United States: risk factors for hospitalization and mortality. *BMC Nephrol*. 2003; 4.
- Olesen J, Lip G, Kamper A, Hommel K, Køber L, Lane D, et al. Stroke and Bleeding in Atrial Fibrillation with Chronic Kidney Disease. *New England Journal of Medicine*. 2012; 367: 625-635.
- Hughes M, Lip G. Stroke and thromboembolism in atrial fibrillation: A systematic review of stroke risk factors, risk stratification schema and cost effectiveness data. *Thromb Haemost*. 2008.
- Zimmerman D, Sood M, Rigatto C, Holden R, Hiremath S, Clase C. Systematic review and meta-analysis of incidence, prevalence and outcomes of atrial fibrillation in patients on dialysis. *Nephrology Dialysis Transplantation*. 2012; 27: 3816-3822.
- Collins A, Foley R, Chavers B, Gilbertson D, Herzog C, Johansen K, et al. US Renal Data System 2011 Annual Data Report. *American Journal of Kidney Diseases*. 2012; 59: A7.
- Hart R, Eikelboom J, Ingram A, Herzog C. Anticoagulants in atrial fibrillation patients with chronic kidney disease. *Nature Reviews Nephrology*. 2012; 8: 569-578.
- Genovesi S, Pogliani D, Faini A, Valsecchi M, Riva A, Stefani F, et al. Prevalence of Atrial Fibrillation and Associated Factors in a Population of Long-Term Hemodialysis Patients. *American Journal of Kidney Diseases*. 2005; 46: 897-902.
- Chen J, Lin L, Yang Y, Hwang J, Chen P, Lin J. Anti-platelet or anti-coagulant agent for the prevention of ischemic stroke in patients with end-stage renal disease and atrial fibrillation-A nation-wide database analyses. *International Journal of Cardiology*. 2014; 177: 1008-1011.
- Drew D, Sarnak M. Ischemic and Hemorrhagic Stroke: High Incidence in Hemodialysis and Peritoneal Dialysis Patients. *American Journal of Kidney Diseases*. 2014; 63: 547-548.
- Reynolds M, Fahrenbach K, Hauch O, Wygant G, Estok R, Cella C, Nalysnyk L. Warfarin Anticoagulation and Outcomes in Patients with Atrial Fibrillation. *Chest*. 2004; 126: 1938-1945.
- Hylek E, Go A, Chang Y, Jensvold N, Henault L, Selby J, Singer D. Effect of Intensity of Oral Anticoagulation on Stroke Severity and Mortality in Atrial Fibrillation. *New England Journal of Medicine*. 2003; 349: 1019-1026.
- Keskar V, Sood M. Use of Oral Anticoagulation in the Management of Atrial Fibrillation in Patients with ESRD: Con. *Clinical Journal of the American Society of Nephrology*. 2016; 11: 2085-2092.
- Dahal K, Kunwar S, Rijal J, Schulman P, Lee J. Stroke, Major Bleeding and Mortality Outcomes in Warfarin Users with Atrial Fibrillation and Chronic Kidney Disease: A Meta-Analysis of Observational Studies. *Chest*. 2016; 149: 951-959.
- Luo G, Ducey P, McKee M, Pinero G, Loyer E, Behringer R, et al. Spontaneous calcification of arteries and cartilage in mice lacking matrix GLA protein. *Nature*. 1997; 386: 78-81.
- O'Neal W, Tanner R, Efrid J, Baber U, Alonso A, Howard V, et al. Atrial fibrillation and incident end-stage renal disease: The Reasons for Geographic

- and Racial Differences in Stroke (REGARDS) study. *International Journal of Cardiology*. 2015; 185: 219-223.
16. Platonov P, Mitrofanova L, Orshanskaya V, Ho S. Structural Abnormalities in Atrial Walls are Associated with Presence and Persistency of Atrial Fibrillation but not with Age. *Journal of the American College of Cardiology*. 2011; 58: 2225-2232.
 17. Salim S, Akula Y, Kandhuri S, Afshan S, Zsom L, Dixit M, Fulop T. Successful Peritoneal Dialysis in Large-Weight Subjects: Clinical Features and Comparisons with Normal-Weight Subjects. *Advances in Peritoneal Dialysis*. 2016; 32: 61-67.
 18. Independent predictors of stroke in patients with atrial fibrillation: A systematic review. *Neurology*. 2007; 69: 546-554.
 19. Hung P, Huang Y, Hsiao C, Sung P, Guo H, Tsai K. Young stroke patients are at high risk for subsequent end-stage renal disease: A population-based observational study. *Nephrology Dialysis Transplantation*. 2014; 29: 873-878.
 20. Wang H, Hung S, Sung J, Hung K, Wang J. Risk of Stroke in Long-term Dialysis Patients Compared With the General Population. *American Journal of Kidney Diseases*. 2014; 63: 604-611.
 21. Skanes A, Healey J, Cairns J, Dorian P, Gillis A, McMurtry M, et al. Focused 2012 Update of the Canadian Cardiovascular Society Atrial Fibrillation Guidelines: Recommendations for Stroke Prevention and Rate/Rhythm Control. *Canadian Journal of Cardiology*. 2012; 28: 125-136.
 22. Wu C, Tsai C, Kor C, Tarng D, Lian I, Yang T, et al. Stroke and Risks of Development and Progression of Kidney Diseases and End-Stage Renal Disease: A Nationwide Population-Based Cohort Study. *PLOS ONE*. 2016; 11.
 23. Muntner P. The Contribution of Increased Diabetes Prevalence and Improved Myocardial Infarction and Stroke Survival to the Increase in Treated End-Stage Renal Disease. *Journal of The American Society of Nephrology*. 2003; 14: 1568-1577.
 24. Genovesi S, Vincenti A, Rossi E, Pogliani D, Acquistapace I, Stella A, Valsecchi M. Atrial Fibrillation and Morbidity and Mortality in a Cohort of Long-term Hemodialysis Patients. *American Journal of Kidney Diseases*. 2008; 51: 255-262.
 25. Tanner R, Calhoun D, Bell E, Bowling C, Gutierrez O, Irvin M, et al. Incident ESRD and Treatment-Resistant Hypertension: The Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study. *American Journal of Kidney Diseases*. 2014; 63: 781-788.