Electrolyte’s imbalance role in atrial fibrillation: Pharmacological management

Saira Rafaqat1*, Sana Rafaqat1, Huma Khurshid1 and Simon Rafaqat2

Abstract
The contribution of the perpetuation of atrial fibrillation is caused by electrical remodeling in which calcium, sodium and potassium channels could refer to changes in the ion channel protein expression, development of fibrosis, gene transcription and ion channel redistribution. Calcium and magnesium could influence the risk of atrial fibrillation which is the leading cause of cardiac death, heart failure and ischemic stroke. The elevated serum concentration of calcium had a higher range of in-patient’s mortality, increased total cost of hospitalization and increased length of hospital stay as compared to those without hypercalcemia in atrial fibrillation patients. Moreover, chloride channels could affect homeostasis, atrial myocardial metabolism which may participate in the development of atrial fibrillation. Up to a 50% risk of incidence of AF are higher in which left ventricular hypertrophy, sudden cardiovascular death and overall mortality relate to a low serum magnesium level. Additionally, magnesium prevents the occurrence of AF after cardiac surgery, whereas greater levels of serum phosphorus in the large population-based study and the related calcium–phosphorus products were linked with a greater incidence of AF. Numerous clinical studies had shown the high preoperative risk of AF that is linked with lower serum potassium levels. The conventional risk factor of increased risk of new onset of AF events could independently link with high dietary sodium intake which enhances the fibrosis and inflammation in the atrium but the mechanism remains unknown. Many drugs were used to maintain the electrolyte imbalance in AF patients.

Keywords: AF, Electrolytes, Calcium, Chloride, Magnesium, Phosphorus, Potassium, Sodium

Background
The most common cardiac arrhythmia is atrial fibrillation (AF) which increased the risk of stroke, heart failure and cardiovascular death [1]. There are many risk factors for the development of AF including age, heart failure, hypertension, coronary heart disease, white race, left ventricular hypertrophy, chronic kidney disease (CKD), obesity and certain lifestyle factors [2]. The contribution of the perpetuation of AF is caused by electrical remodeling in calcium, sodium and potassium channels which could refer to changes in the ion channel protein expression, development of fibrosis, gene transcription and ion channel redistribution [3].

Calcium and magnesium could influence the risk of atrial fibrillation which is the leading cause of cardiac death, heart failure and ischemic stroke [4]. In the same way, Alonso et al.’s study had reported the relationship of AF and the burden of supraventricular arrhythmias with circulating electrolytes including calcium, sodium, phosphorous, magnesium, potassium and chlorine. The data are scarcer that explain the relationship between the risk of AF with circulating electrolytes such as potassium, chlorine, calcium and sodium, whereas the increased risk of AF has been related to a higher concentration of phosphorous and lower circulating magnesium concentration. Moreover, the authors had observed a lower prevalence of...
AF among persons with elevated levels of circulating potassium, chloride, phosphorous and magnesium [5].

In the general population, approximately 3% of AF occurring is the well-known risk factor of cardiovascular morbidity and mortality. In the renal failure population, non-valvular AF frequently occurs ranging from 19 to 24% rising to 27% in patients with end-stage renal disease. Numerous studies have implicated atrial fibrillation as a contributing factor in CKD as well as cardiovascular events. The prevalence of coronary artery disease (CAD) in patients with AF varies substantially from 17 to 46% [6].

Google Scholar, PubMed and Science direct were used to review the literature. October 20, 2021, was the late date of the research. Many keywords were used for searching the literature such as AF, electrolytes, calcium, chloride, magnesium, phosphorus, potassium and sodium. The language of clinical studies was restricted to English. This review article focuses to report the recent studies which mainly explained the role of electrolytes (calcium, chloride, magnesium, phosphorus, potassium and sodium) imbalance in AF patients as explained in Fig. 1 and their pharmacological management in AF subjects.

Main text
Role of different electrolytes imbalance in AF
There are many electrolytes which are present in the human body; however, this review article only highlights pathophysiological aspects of major electrolytes such as calcium, chloride, magnesium, phosphorus, potassium and sodium in AF as explained in Fig. 2 and also report the drug management of electrolytes imbalance in AF subjects.

Calcium
Calcium is very important in regulating heartbeat and fluid balance within cells, muscle contraction, oocyte activation, building strong bones and teeth, nerve impulse, transmission and blood clotting within cells. Their requirements are increased during the period of growth including in childhood, during pregnancy and breastfeeding [7].

The intracellular calcium overload was involved in the development of electrical remodeling. It was also suggested to be involved in electrical remodeling largely based on indirect evidence using L-type calcium channel antagonists [8, 9]. In the process of electrical remodeling, mitochondrial calcium accumulation has been implicated
because mitochondria can buffer large increases in intracellular calcium when cytoplasmic free calcium reaches pathologically high micromolar levels [10].

Small conduction calcium-activated potassium channels are propagated of triggered impulses from the pulmonary veins to the atria that are caused by calcium. The expression of these channels increased due to the rapid stimulation. In the pulmonary veins, an action potential is shortened. Within the atria, heart failure has resulted because of the structural changes and remodeling of calcium cycling which support persistent atrial fibrillation [11]. Hypercalcemia is linked with left ventricular hypertrophy, shortened QT interval, hypertension, vascular calcification and arrhythmias. On the other way, hypocalcemia is related to prolonged QT intervals, heart failure and life-threatening cardiac arrhythmias. Both decreased and increased serum concentrations of calcium are linked with increased mortality [3].

According to the previous studies, AF risk is increased due to a rapid atrial activation rate which induces electrical remodeling. This remodeling consists of upregulation of sodium-calcium exchanger, Ca^{2+} transients are reduced, and reduction of L-type Ca^{2+} current and sarcoplasmic reticulum function altered, characterized by the increased spontaneous Ca^{2+} sparks as well as waves, have been attribution to hyperactive RyR2 channels that possibly as a result of elevated phosphorylation at residues Ser2808 and Ser2815. These increased Ca^{2+} waves as well as leaky RyR2 channels are capable of focal atrial electrical activity and are also triggered delayed after afterdepolarization. Therefore, the most important contributor to the induction and maintenance of AF was the hyperactive RyR2 channels in humans [12].

Deo M et al.’s study had reported in cardiac cells; intracellular calcium dynamics have been recognized as an important contributor in life-threatening ventricular arrhythmia including ventricular fibrillation as well as ventricular tachycardia and increasing the prevalent atrial arrhythmias such as flutter and atrial fibrillation [13].

In the same way, Abed et al.’s study had described the elevated serum concentration of calcium concentration had an elevated range of in-patient’s mortality, increased total cost of hospitalization and increased length of hospital stay as compared to those without hypercalcemia in
AF patients. Moreover, the authors have suggested further investigation on the role of calcium serum levels in patients with AF, both as a marker to predict mortality and as a key target of the in-patient therapeutic approach [14].

In AF patients, there are drugs including calcium channel blockers, diltiazem such as Cardizem and verapamil including Calan and Isoptin for the effective for initial ventricular rate control. They have given intravenously in bolus doses until the ventricular rate becomes slower [15]. Also, Heywood et al.‘s study stated that calcium channel blockers could have a role in the acute reduction of ventricular response in AF patients that had complications due to heart failure; however, their safety in chronic heart rate control remains to be proven [16].

Moreover, Chao et al. revealed in the nationwide AF cohort, those patients receiving rate control treatment with calcium channel blockers or β-blockers had reduced risk of mortality, whereas it was also associated with the largest risk reduction with the use of β-blockers and greater mortality was linked with the use of digoxin. However, to confirm these findings, randomized and prospective trials are required [17].

At the cell membrane, verapamil acts to inhibit transmural fluxes of calcium that slow ventricular response in AF by inhibiting the atrioventricular conduction. When serum calcium level rises to abnormal levels, this effect is abolished in AF patients and slowing of the ventricular response is achieved by reducing serum calcium, whereas verapamil treatment was maintained [18].

Chloride

After sodium, the most abundant electrolytes in serum is the chloride which has a key role in the regulation of body fluids, acid-base status, electrolyte balance, and the preservation of electrical neutrality. Also, it is an essential component for the assessment of various pathological conditions. Abnormal chloride levels play role in more serious underlying metabolic disorders including alkalosis or acidosis [19].

Atrial fibrillation begins from paroxysmal to progressing form through persistent to permanent type with structural and electrical atrial remodeling [20, 21]. The maladaptive process is the left atrial remodeling which includes collagen accumulation, apoptosis, fibroblast proliferation and myocytes hypertrophy [22]. In addition, various studies had focused on the processes responsible for atrial fibrillation changes in the ion channels in the cell membrane and also in the electrophysiological properties of atrial tissues. It has been reported that in the atrial myocytes changes in the channels mainly include Ca$^{2+}$, K$^+$ and Na$^+$ ion channels [23].

Moreover, the function of chloride channels involves cell volume regulation, regulation of excitability, ionic homeostasis, transepithelial transport, etc., in the plasma membrane [24]. Duan et al. reported that the chloride channel was related to various cardiovascular diseases including hypertension, ischemic, myocardial hypertrophy and heart failure [25].

The evidence of the significance of chloride intracellular channel 4 (CLIC4) was involved in cellular differentiation, endothelial tubulogenesis, apoptosis and inflammation. CLIC4 expresses in cardiomyocytes, lung alveolar septae and vascular endothelial cells [26]. By modulating mitochondrial function, chloride channels play an important role in cardioprotection from ischemic-reperfusion injury and cardiac function. Additionally, Jiang et al.‘s study demonstrated the upregulated CLIC1,4,5 is differentially expressed in patients with atrial fibrillation. The authors indicate in results that chloride channels could affect homeostasis, atrial myocardial metabolism and also participate in the development of atrial fibrillation [27].

In the same way, Kolkebeck et al.‘s study was determined whether calcium chloride (CaCl (2)) pretreatment would blunt an SBP drop after i.v. diltiazem, while allowing diltiazem to maintain its efficacy. A prospective, randomized, double-blind, placebo-controlled study was conducted. Although i.v. CaCl (2) seems to be equally safe compared to placebo as a pretreatment in the management of atrial fibrillation or flutter (AFF) with the rapid ventricular response (RVR), the authors were unable to find a statistically significant blunting of SBP drop with CaCl (2) i.v. pretreatment. Until further research determines, a benefit exists. Moreover, authors cannot recommend i.v. CaCl (2) pretreatment before diltiazem in the treatment of AFF with rapid ventricular response [28].

Also, Jiang et al.‘s study had indicated that chloride intracellular channels (CLICs) play an important role in the development of atrial fibrillation. Chloride intracellular channels and structural type IV collagen may interact with each other to promote the development of AF in rheumatic mitral valve disease [27]. Hansen et al.‘s study had explained the quantitative PCR experiments using human heart tissue from healthy donors demonstrated that CLCN2 is expressed across all four heart chambers. Authors explain the genetic and functional data points to a possible link between loss of CIC-2 function and an increased risk of developing AF [29]. The novel finding
is that intracellular chlorine accumulation is induced by rapid pacing and may play a role in AF pathogenesis by causing resting membrane depolarization and effective refractory period (ERP) reduction [30].

**Magnesium**

The fourth most important and abundant cation is the magnesium in the human body as well as intracellular tissues and also the second most prevalent cation. Many physiologic roles of magnesium involve in protein transport, enzyme activity and become an essential part of all adenosine triphosphate-utilization systems. It is related to cardiovascular disorders; for example, reducing dietary intake of magnesium has been related to a higher risk of AF, hypertension, ischemic heart disease, heart failure-related hospitalization and new-onset heart failure. On the different organ systems, magnesium has various significant pharmacological as well as physiological effects that involve the mechanism of action such as membrane stabilization, calcium antagonism and regulation of energy transfer [31].

Moreover, up to a 50% risk of incidence of AF are higher, in which left ventricular hypertrophy, sudden cardiovascular death and overall mortality relate to a low serum magnesium level. Intravenous magnesium directly affects myocardial potassium channels, prolongs the PR interval, has voltage-dependent and indirect effects on sodium and calcium channels and elevated the refractory period of antegrade atrioventricular node conduction [32, 33].

Misialek et al. reported that the increased risk of cardiovascular disease (CVD) is linked with low serum magnesium that includes ventricular arrhythmias. In conclusion, the authors showed that a higher risk of atrial fibrillation was related to low serum Mg, not with dietary Mg [34].

Additionally, Crippa and Rasmussen’s studies had reported that intravenous magnesium has a high therapeutic to toxic ratio and minimal negative inotropic effects [35, 36]. It is also reduced the automaticity [37], atrioventricular nodal conduction, digoxin-induced arrhythmias and prolonged QT interval which are caused by polymorphic ventricular tachycardia. The occurrence of AF after cardiac surgery could also be reduced due to the prophylactic use of intravenous magnesium. Intravenous magnesium as compared to other antiarrhythmic agents or with digoxin is not effective in converting acute onset AF to sinus rhythm in subjects with a normal serum magnesium concentration [38]. Also, Miller et al.’s study has been demonstrated a meta-analysis that shows magnesium in preventing the occurrence of AF after cardiac surgery [39].

Various studies had reported a significant association between a higher risk of postoperative atrial fibrillation (POAF) and low preoperative intracellular magnesium concentrations [40, 41]. The 16 percent was a range of incidence of postoperative atrial fibrillation. The multivariate risk of postoperative AF was increased fivefold due to the rate of myocardial extraction of intracellular magnesium which was ≥7% that might be a new and potent predictive factor for postoperative AF [40].

In the same way, Henyan et al. had suggested that the risk of POAF was reduced due to the lower doses of magnesium (OR 0.36, 95% CI 0.23–0.56). On the other hand, moderate-high doses did not reduce the risk of postoperative AF (OR 0.99, 95% CI 0.70–1.42), whereas no trials have directly compared the impact of either various magnesium dosing strategies or timing on postoperative atrial fibrillation risk and it gave a significant knowledge gap [42].

The development of AF in individuals without CVDs is linked to the lower serum magnesium because hypomagnesemia is common and is associated with AF which could have potential clinical implications [43]. Moreover, a meta-analysis had revealed that the incidence of postoperative AF was about 36 percent due to the reduced intravenous magnesium [44].

Furthermore, Tercius et al.’s study had demonstrated that concurrent use of magnesium enhances the ability of ibutilide to successfully convert AF or flutter. The greatest benefit had appeared due to the 4 g of magnesium dose. Previous studies had been reported the relationship of increased risk of postoperative atrial fibrillation (POAF) with hypomagnesemia [45]. In contrast, Klinger et al.’s study had concluded that the incidence of new-onset POAF after cardiac surgery does not decrease due to the high-dose intraoperative Mg therapy [46]. Moreover, Rajagopalan et al.’s study had concluded that Mg infusion does not increase the rate of successful cardioversion in patients undergoing electric cardioversion for persistent AF [47].

In the same way, Arsenault et al.’s study had reported the reduced risk of postoperative AF with oral magnesium supplementation [48], whereas Larsson et al.’s study revealed in Mendelian randomization analysis to show high genetically determined circulating magnesium which was related to reducing the atrial fibrillation risk [49].

For years in clinical medicines, to stop or treat arrhythmias, magnesium supplements play their role by preventing atrial fibrillation following cardiac surgery, refractory ventricular fibrillation, acute treatment of rapid AF, new-onset and treatment-refractory supraventricular tachycardia (SVT), and a variety of drug-induced arrhythmias including torsade de points.
(TdP); magnesium has been incorporating into their recent guidelines for managing as well as preventing certain arrhythmias [50].

Furthermore, Ho et al.'s study had reported in a meta-analysis showing that adding intravenous magnesium to either ibutilide or digoxin was not effective in achieving sinus rhythm once atrial fibrillation has developed. As a result, the therapeutic effect of intravenous magnesium is mainly on reducing the fast ventricular response rate in subjects with acute AF [38].

Phosphorus
Phosphorus is an essential mineral that is naturally present in many foods and available as a dietary supplement. Phosphorus is a component of bones, teeth, DNA, and RNA [51]. It is important for many biologic functions, such as energy exchange, cellular signal transduction as well as mineral metabolism and also is an independent predictor of atrial fibrillation [52].

Various studies have been reported that elevated phosphorus levels were associated with coronary arteries, increased left ventricular mass, carotid atherosclerosis, increased arterial stiffness and calcification of the aorta [53–59]. It also increased cardiovascular mortality and morbidity in patients with and without chronic kidney diseases [55, 57, 60, 61]. Lopez et al.'s study had concluded the greater levels of serum phosphorus in the large population-based study and the related calcium–phosphorus products were linked with a greater incidence of AF [62].

Numerous potential processes could explain the greater phosphorus levels with increased risk of AF. Firstly, coronary arteries and calcification of the aorta had been associated with the excess phosphorus levels [58, 59], thereby directly promoting vascular injury, smooth muscle proliferation and elevated vascular calcification which can lead to a greater risk of AF. Secondly, the inhibition of 1,25-dihydroxy vitamin D synthesis is caused due to the high levels of phosphorus [63] and it has been hypothesized that decreased cardiac contractility, as well as increased coronary calcification, could cause the lower levels of 1,25-dihydroxy vitamin D [64, 65], which might lead to the increased risk of AF. Thirdly, secondary hyperparathyroidism has been linked to excess phosphorus which might involve increased circulating levels of parathyroid hormone which in return could increase the proinflammatory processes that lead to an increased risk of AF. Similarly, a recent cross-sectional study also demonstrated that parathyroid hormone levels were elevated in patients with atrial fibrillation as compared to controls in sinus rhythm [66].

Various mechanisms could mediate the relationship between AF and serum phosphorus levels, such as the greater risk of heart failure and increased left ventricular mass in those with elevated phosphorus concentrations [55]. Finally, a phosphate-regulating hormone, fibroblast growth factor 23, reflects serum phosphorus levels that had been linked with left ventricular dysfunction and the prevalence of AF in patients undergoing coronary angiography [67].

Potassium
Potassium (K) is an important macrominerals nutrient and principal cation in intracellular fluid, which regulates the osmotic pressure; muscle contraction participates in acid–base balance, cell membrane function and more in human. A high dietary intake of potassium has a protective role against the kidneys, cardiovascular system and bones diseases [68].

The risk of cardiovascular disease has increased especially cardiac arrest and ventricular arrhythmias that had shown an association with serum potassium (<3.5 mmol/l), especially in hypokalemia [69]. Various studies had reported the relationship between the risk of AF and serum potassium. Moreover, numerous clinical studies had shown that the high preoperative risk of AF was linked with lower serum potassium levels [70, 71]. However, other populations studies did not show an association between them [72, 73]. Additionally, Severi et al.'s study found decreased serum potassium to increase in p-wave duration which is a marker of atrial conduction in hemodialysis patients [74].

Moreover, Krijthe et al.'s study also reported a link between increased risk of AF with hypokalemia (<3.50 mmol/l) in comparison with normokalemia [75]. Moreover, Auer et al.'s study had revealed a relationship of lower serum potassium (<3.9 mmol/l) with increased risk of AF during the postoperative period [71]. Numerous studies had been investigated the influence of potassium in the progress of AF. Wahr et al.'s study explained among 2402 patients undergoing cardiac surgery reports the association of AF with preoperative hypokalemia (<3.5 mmol/l) as compared to elevated levels of AF [70]. Also, Madias et al.'s study stated the higher risk of AF was not linked with hypokalemia during hospitalization as compared to normokalemia and included 517 patients with acute myocardial infarction. The most likely mechanism through which increased risk of AF was caused due to serum potassium, which includes the influence of potassium on the cell membrane potential, cellular hyperpolarized, hasten depolarization and increased resting potential triggered due to the low serum potassium levels [72, 76].

In the same way, Worthley et al.'s study stated the resting membrane potential is happened due to the extracellular potassium concentration; therefore, it has a large impact on myocardial tissue excitability. Intravenous
potassium is often used to treat hypokalaemia cardiac arrhythmias as the cardiac effects of hypokalaemia include excitability and contractility changes [77].

The anatomical or functional obstacle is caused due to initiation of re-entry, rise ectopic beats that resulted in the abnormal excitability in myocardial cells. The repolarization process of the cardiac action potential (AP) is controlled by potassium currents, membrane potential, refractoriness of the myocardium which is also determined by potassium channel functions. Both loss and gain of the potassium channel function could lead to arrhythmia. These are three pathophysiological relevant aspects that pro-arrhythmic consequences of malfunction potassium channels in atria and ventricular tissue. It has been resulted due to drug action, disease-induced remodeling and genetic background. The increased risk of sudden cardiac death is due to heart failure and the downregulation of potassium channels. Polymorphism and mutations in genes encoding for atrial potassium channels could be linked with loss of function, gain of function and shortened and prolonged action potential duration. The particular therapeutic challenge has become due to the block of atrial potassium channels when trying to better atrial fibrillation. This arrhythmia has a strong tendency to cause electrical remodeling that affects various potassium channels [78].

Additionally, Tazmini et al.'s study had reported that increasing plasma-potassium levels did not significantly enhance the conversion of recent-onset atrial fibrillation (ROAF) or atrial flutter to sinus rhythm in subjects with potassium levels in the lower-normal range; authors revealed in results that treatment could be effective when a rapid increase in potassium levels is achieved and tolerated [79].

Sodium
Sodium allows to build up an electrostatic charge on cell membranes as well as transmission of nerve potential when the charge is allowed to dissipate by a moving wave of voltage change in the organism. It is also classified as a dietary inorganic micromineral for animals [80]. Moreover, Frisoli et al.'s study had stated the independent relation of blood pressure and high salt intake that could increase the risk of heart failure, stroke, proteinuric renal disease and left ventricular hypertrophy (LVH) [81].

The conventional risk factor of increased risk of new onset of atrial fibrillation events is independently linked with high dietary sodium intake. They had reported the first study about the relationship between the cumulative incidence of AF events and dietary sodium intake. It is also possible that AF is connected with sodium intake which enhances fibrosis and inflammation in the atrium but the mechanism remains unknown [82]. Similarly, Cavusoglu et al.'s study reported that hyponatremia was independently related to the occurrence of atrial fibrillation [83].

The occurrence of AF had increased the hypokalemia and hyponatremia. Pulmonary veins and sinoatrial nodes play a critical role in the pathophysiology of AF. So, low sodium, as well as low potassium, was differentially modulated pulmonary veins and sinoatrial node electrical properties. Low sodium and low potassium-induced slowing of sinoatrial node beating rate and genesis of pulmonary veins burst firing which could contribute to the higher occurrence of AF during hyponatremia or hypokalemia [84]. In addition, Takase et al.'s study also highlights the association of salt intake with the presence and development of AF in the general population, including other factors rather than salt intake had a much more prominent impact on the progress of AF. Further, the authors had been suggested the complementary role of salt intake for the prediction of atrial fibrillation [85].

There are certain clinical entities, including chronic heart failure, pneumonia, coronary artery bypass surgery, chronic kidney disease and hypomagnesemia, all of which could result in hyponatremia which also predispose the patient to the process of atrial fibrillation. There was a strong negative correlation between serum sodium level and heart rate. The main cause of hyponatremia was the reason for the high ventricular rate in patients with lower concentrations of sodium that blocks the inhibitor function of the AV node on accessory pathways [86].

Various clinical cardiac disorders are linked with the rise of the intracellular Na concentration (Na⁺) in heart muscle. A clear example is the digitalis toxicity in which excessive inhibition of the NA/K pump causes the raised of sodium concentration as compared to a normal level. Moreover, the rise of sodium concentration could be an important contributor that caused to increase the cardiac arrhythmias [87].

Oulu project Elucidating Risk of Atherosclerosis (OPERA) cohort study had been evaluated the relationship between the incidence of new-onset AF and dietary sodium intake during a mean follow-up of 19 years among 716 subjects. The main finding indicates that the long-term risk of new-onset AF was linked to sodium intake but further confirmatory studies are required [82]. Moreover, Dudenbostel et al. demonstrated a significant relationship between AF in PA patients with a lower 24-h urinary sodium-to-potassium ratio (24hUNak). There were benefits for an increase in potassium, and reduction in sodium has been shown in patients with hypertension. Using the UNak ratio as a tool that improves through medical therapy and diet including mineralocorticoid receptor antagonism could be key to stopping atrial fibrillation [88].
Serious complications have been reported due to the AF including thromboembolism, congestive heart failure and myocardial infarction. To prevent the adverse consequences of AF, it is important to recognize and acute management of AF in the physician's office or emergency department [89]. There is the majority of antiarrhythmic drugs available that exert predominant effects on cardiac potassium or sodium currents. The membrane-stabilizing agents are sodium channel blocking drugs because the excitability of cardiac tissue is decreased by them. Quinidine, as well as disopyramide, affects conduction including sodium channel blockade in case of rapid heart rates. Also, these drugs have intermediate sodium channel blocking activity and exhibit use dependence. These agents largely affect potassium channels (I_{Kr}) at normal or slow heart rates, low concentrations and also display reverse use dependence for potassium [90].

A century ago, Quinidine was used as a potential antiarrhythmic drug. It is a vagolytic and blocking agent with an intermediate sodium channel blocking effect at rapid heart rates, higher concentration, at slower heart rates, has potassium channel blocking effect and normal concentration and is rarely used for AF. Disopyramide drugs blocking the sodium channel and prescriptions represent 1% to 2% of annual antiarrhythmic drug prescriptions in the USA [91]. Without structural heart disease, flecainide and propafenone are recommended for the management of patients with atrial fibrillation [92].

At present, it is represented 10% of annual US antiarrhythmic drug prescriptions. Flecainide has a significant activity for sodium channel blocking and has mild I_{Kr} blocking effects but is not related to significant QT prolongation. It has mild negative inotropic effects and like propafenone, and it is linked with a significant incidence of atrial flutter [90, 93, 94].

**Conclusion**

This review concludes that electrolyte imbalance plays a significant role in the pathogenesis of atrial fibrillation. To manage the electrolyte imbalance in AF subjects, numerous drugs were used. Future studies need to find the exact mechanism of these electrolytes in AF. More research studies are required to find the diet management of these electrolytes in AF subjects.

**Abbreviations**

AF: Atrial fibrillation; CLIC4: Chloride intracellular channel 4; CVD: Cardiovascular disease; POAF: Postoperative atrial fibrillation; LVH: Left ventricular hypertrophy; SVT: Supraventricular tachycardia.

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**Author details**

1. Lahore College for Women University, Near Wapda Flats, Jail Rd, Jubilee Town, Lahore 54000, Punjab, Pakistan. 2. Forman Christian College (A Chartered University), Zahoor Elahi Rd, Gulberg III, Lahore 54600, Punjab, Pakistan.

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