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DIGOXIN IN ATRIAL FIBRILLATION : A PHARMACOKINETIC PERSPECTIVE

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Abstract
Atrial fibrillation (AF) is a common cardiac arrhythmia associated with an increased risk of stroke and heart failure. Digoxin, a cardiac glycoside, has been a cornerstone in the management of AF for decades. This literature review explores the utilization of digoxin in atrial fibrillation, with a specific focus on its pharmacokinetic properties. Additionally, it discusses the challenges and concerns associated with digoxin's pharmacokinetics, including its narrow therapeutic window and the impact of patient-specific factors such as age, renal function, and drug interactions. This review highlights the importance of precise dosing and therapeutic drug monitoring to ensure both safety and efficacy in AF patients treated with digoxin. It also underscores the need for further research and clinical guidelines to optimize digoxin's use in the contemporary management of atrial fibrillation.

Keywords:- Atrial Fibrillation, Digoxin, Pharmacokinetics

1.0 Introduction

Atrial fibrillation (AF) is an atrial tachyarrhythmia characterized by uncoordinated atrial activation with consequent deterioration of atrial mechanical function (Academy of Medicine Malaysia 2012). In electrocardiogram (ECG) surface, AF pattern can be seen by irregular RR intervals and the absence of any distinct P waves that are replaced by fibrillary (F) waves. Clinically there are five types of atrial fibrillation which are diagnosed based on the presentation and the duration of the episode. The classifications of AF includes first diagnosed AF, paroxysmal AF, persistent AF, long standing persistent AF and permanent AF (Kirrchof P. et al 2016).

AF is the most common sustained cardiac arrhythmia encountered in clinical practice. The estimated numbers of men and women with AF were 20.9 million and 12.6 million respectively, with developed countries contributed higher incidence and prevalence rsates. (Freestone B. et al (2003); Koh K.T. et al 2019). By 2030, there is an expectation that about 120 000-215 000 new cases diagnosed with AF will be reported per year in European Union (Kirchhof P. et al 2016) and the number will likely to increase several-fold by 2050 (Shenasa et al. 2014). According to the CDC WONDER Online

Database, AF was included on 183,321 death certificates in 2019 and was the primary factor in 26,535 of those mortalities.

The risks of both cerebral stroke and heart failure are increased nearly five-fold in patients with AF, and about 20% of every stroke may be associated with this condition. (Sethi NJ et al. 2018). According to Flint AC et al. (2012), this arrhythmia may be the root cause of more than 70,000 ischemic strokes per year, accountable for 10%–12% of all ischemic strokes in the United States. These complications impose a substantial burden on patients' health and necessitating comprehensive medical management. Financially, the costs associated with the treatment and management of AF, including medications, medical procedures, and hospitalizations, can be substantial, placing financial strain on both individuals and healthcare systems. Moreover, AF can detrimentally impact quality of life by inducing symptoms like palpitations, fatigue, and breathlessness, limiting physical activities, and increasing the risk of depression and anxiety.

Digoxin is a medication that has played a significant role in the management of atrial fibrillation, a common cardiac arrhythmia characterized by irregular and often rapid heartbeats. Digoxin is a cardiac glycoside derived from the foxglove plant, *Digitalis purpurea*, and it works by increasing the force of contraction of the heart muscle, thereby slowing down the heart rate and improving its overall efficiency. While digoxin has been used for decades, its pharmacokinetics present important concerns in clinical practice. Its narrow therapeutic window requires careful dosing and monitoring to avoid toxicity. Furthermore, factors such as age, renal function, and drug interactions can significantly impact its pharmacokinetics, necessitating precise management to ensure both safety and efficacy in patients with atrial fibrillation.

2.0 Risk factors of AF

There are several risk factors contributing to the development of atrial fibrillation. AF cases are more prominent in adults aged above 20 years old and its incidence is increasing with age. Besides that, adverse lifestyle factors including smoking, significant alcohol intake, obesity and patients particularly with underlying diseases such as hypertension, pulmonary disease, hypothyroidism heart failure, coronary artery disease (CAD), valvular heart disease, obesity, diabetes mellitus or chronic kidney disease (CKD) will increase the likelihood to be diagnosed with AF. In terms of gender, the age-adjusted incidence and prevalence of AF are commonly seen in men but the death risk is similar or much higher in women. (Shenasa et al. 2014; Kirchhof P. et al 2016).

3.0 Classification of AF

AF can be categorized in light of its etiology, symptoms, whether it happens with or without recognisable cause in people with a heart that is anatomically normal in the presence of abnormal heart structure. The most prominent and often acknowledged classification approach for AF is based on temporal rhythm proposed by the association of American College of Cardiology (ACC) and European Society of Cardiology (ESC). There are four dominant categories discovered in this scheme which are presented in Table 1. The classification includes the first detected is also known as lone AF, paroxysmal (PAF), persistent (PeAF) and permanent AF. Lone AF occurs in patients below 60 years old when structural cardiac disease is absent or systemic hypertension. The episodes of AF can be paroxysmal, if they terminate voluntarily within 7 days without intervention, persistent if episodes last for more than seven days usually necessitating electrical or drug cardioversion in order to terminate. Whereas, when termination is unsuccessful by long-standing (more than a year) AF with cardioversion, wherein cardioversion is not desired or has never been tried, is known as permanent AF.

Classification	Definition
Paroxysmal AF	● Terminates spontaneously or with intervention in < 7 days ● Recurrent episodes may occur
Persistent AF	● Continuous AF duration > 7 days
Longstanding persistent AF	● Continuous AF duration > 12 months
Permanent AF	● Joint decision between patient and clinician not to pursue rhythm control treatment
Nonvalvular AF	● AF in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair

Table 1. Types of AF and definition (Wann LS et al. 2014)

4.0 Mechanisms of AF

In spite of numerous years of investigation, the exact mechanisms of AF inauguration are only partly understood. The "circus movement reentry" and "ectopic focus" hypotheses were the two most popular theories for these mechanisms in the beginning 1900s (Masatoshi Yamazaki et al. 2012). Afterwards, Moe et al demonstrated the ‘‘multiple wavelet hypothesis’’ where the unorganized firing of AF is due to the irregular transmission wavelets (more than 20 wavelets) in a heterogeneous medium of distributed refractoriness in 1962. Early work by Allessie et al. in 1985 was concerned with experimental support for Moe’s theory in a canine model of AF induced in with the presence of acetylcholine. Few independent wavelets transmitted concurrently all over atria. Nevertheless, Allesie concluded AF requires 4 to 6 wavelets to be maintained compared to Moe who predicted a minimum of 26 wavelets are necessary. This disagreement has never been resolved.

5.0 General management of AF

In general, the objective management principles of AF are firstly to relieve its symptoms such as palpitation, dizziness, fatigue and dyspnoea. Second, to prevent serious complications of AF for example thromboembolism (particularly ischaemic stroke) and heart failure. Next, the aim is to enhance proper management of concomitant cardiovascular disease by rate control and correction of rhythm disturbance. As such, optimal medication therapy will be an integral part of the management of AF (Academy of Medicine Malaysia et al. 2012). Pharmacological rate control can be achieved for acute or long-term setting with Beta blockers (Esmolol, Metoprolol, Propranolol), Calcium channel blockers (Diltiazem, Verapamil) and other agent such as Amiodarone and Digoxin (Academy of Medicine Malaysia et al. 2012; Kirrchof P. et al 2016).

There have been fundamental changes on AF treatment over the last 10 years. Rate control and anticoagulation are the mainstays of atrial fibrillation (AF) and rhythm control therapy for patients who are symptomatically constrained by AF (Ferrari R et.al 2016). Drugs that slow the heart rate are known as rate control. Chemical or pharmacologic cardioversion, often known as antiarrhythmic drugs, helps the heart return to normal sinus rhythm and maintain it, are known as rhythm control. Recent research contrasting the rhythm control strategy with the traditional rate control strategy has challenged the long-established approach. Rate control is not inferior to rhythm control with regard to mortality, according to data from five research comparing the two types of control trials (Hohnloser et al 2001; Van gelder et al 2002; Wyse et al 2002; Carlsson et al 2003; Opolski et al 2003) or quality of life (Gronefeld et al 2003).

On the other hand, the largest of these studies (Wyse et al. 2002) found that rhythm control mortality was more prevalent among those with coronary heart disease, those without heart failure, and those over 65. In a separate study by Okcun et al. (2004) comparing rate control with rhythm control, it was discovered that rhythm control was preferred among patients with dilated cardiomyopathy and heart failure. In the rhythm control component of this analysis, there was significant variance in the length, level, and type of anticoagulation, which could have had an impact on the prevalence of stroke and thromboembolism.

In the AFFIRM study (Atrial Fibrillation Follow-up Investigation of Rhythm Management), an insignificant trend towards higher mortality was seen in the rate control group. Of greater importance,

there was no evidence to support the claim that the rhythm-control strategy protected patients from stroke. 4060 participants in the trial who were 65 years or over, had atrial fibrillation that was likely to recur, and were at risk for stroke were randomly assigned to a rhythm control method versus a rate control strategy (Wyse DG et al. 2002). The elevated rates of thromboembolic complications and mortality observed in this cohort are thought to be caused by clinically silent recurrences of AF in the rhythm-control group. This demonstrates how crucial anticoagulation is for patients with rhythm-control and rate-control.

6.0 Digoxin in AF Management

Digoxin, a cardiac glycoside was firstly described by William Withering in 1785 regarding of its use in treating patients in heart failure (Starner D et al. 2008) and during the early of 20th century, the role of Digoxin has been established by James McKenzie and Thomas Lewis as a cornerstone of chronic Atrial Fibrillation (AF) treatment (Tarmago J et al. 2006). The cardenolides has a five- or a six-membered lactone ring attached to a steroid nucleus at 17th position.

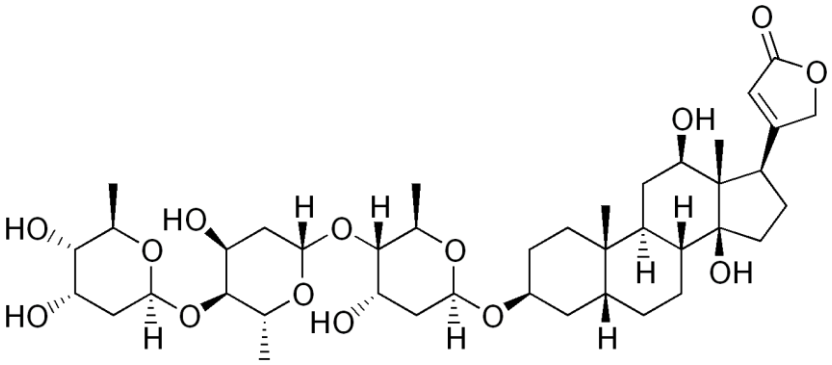


Figure 1. Chemical structure of digoxin (C41H64O14) (Paula Melo et al. 2012)

According to Eric J. Eichhorn and Mihai Gheorghiade, despite the angiotensin-converting-enzyme (ACE) inhibitors and beta blockers' demonstrated survival benefits, digitalis still seems to have a place in our armamentarium for treating heart failure and atrial fibrillation even after 200 years of use. It has played an important role in controlling heart rate in patients with rhythm disturbance for over 50 years (Scalease et al. 2016). The mechanism of action of Digoxin is by inhibition of sodium-potassium-ATPase pump in myocardial cells which results in positive inotropic effects that enhance the vagal tone and reduce sympathetic activation. This may lead to a direct suppression of sinoatrial and atrioventricular nodal conduction that subsequently increase the refractory period, decrease the conduction velocity and lowering the heart rate (DiDomenico R et al. 2017).

Apart from that, digoxin also exerts parasympathomimetic via activation of the vagal efferent nerves in the heart. Digoxin improves ganglionic transmission, sensitizes the afferent system, and improves ganglionic transmission in the efferent vagal nerves, which in turn improves peripheral organ responses to acetylcholine, a neurotransmitter that lowers heart rate. The interaction of the sympathetic and parasympathetic nervous systems due to the stimulation of vagal nerves is thought to restrict the norepinephrine release from sympathetic terminals. Its action on sinus automaticity leads to reduced heart rate and prolongs atrioventricular conduction by reduction of the conduction velocity of electrical impulses through the atrioventricular node (Cheng J.W et al. 2010). Thus, the widely accepted framework of AF mechanism emphasizes on the dependency of triggers and substrate, and monophasic atrial potential recordings illustrate differences between the characteristics of normal myocardium and the substrate of AF, including for new-onset episodes (Filipe Ferrari et al. 2020).

According to European Society of Cardiologist Guideline 2020, Digoxin is among the recommended adjunctive drugs for controlling heart rate in new onset of atrial fibrillation besides beta blocker and non-dihydropyridine (non-DHP) calcium channel blockers. However, it is not outlined as the first preferred choice but only being preserved for severe and refractory cases (Hindricks et al. 2021).

These drugs (monotherapy or a combination thereof) are also recommended in patients with paroxysmal, persistent or permanent AF (Academic of Medicine Malaysia et al. 2012). Administration of Digoxin may be considered in patients with Acute Coronary Syndrome (ACS) and AF associated with severe left ventricular dysfunction (LVEF < 40%) and systolic heart failure or in haemodynamic instability state due to its advantageous of positive inotropic effect (Hindricks et al., 2021; January et al., 2019). Digoxin is now prescribed (class IIb, level of evidence B in European guidelines) for patients with heart failure (HF) with reduced ejection fraction (HFrEF) and sinus rhythm who continue to experience symptoms despite receiving therapy with renin-angiotensin-aldosterone system inhibitors and beta blockers (BBs) (McDonagh TA et al. 2021) , as well as for rate control in patients with HFrEF and AF (Hindricks G et al. 2020). The most often recommended medication for AF in the world persists to be digoxin (Ferrari F.et al. 2020). Clinical trials have shown that at least 54% to 70% of patients with AF are currently receiving Digoxin as part of their therapy (Nguyen T et al. 2016). Digoxin was added for rate control after studies from 2011 and 2015, both of which were published in BMJ Clinical Evidence with systematic reviews, supported this practice when a rate-limiting calcium channel blocker failed to provide appropriate rate control in AF (Whayne TF et al. 2018). The treatment dose of Digoxin as a rate controller in AF are as follows:

Drug Route	Oral	IV/IM	Remark
Total Digitalising Dose (TDD) (mg)	0.75 – 1.5	0.5 – 1.0	● Give ½ (one-half) of the TDD as the initial dose, then give ¼ (one-quarter) of the TDD in each of two subsequent doses at 6 – 8 hours intervals. Obtain ECG 6 hours after each dose to assess potential toxicity. ● Do not give full TDD at once. ● Clinical response should be fully evaluated prior to additional doses (eg: ECG)
Daily maintenance dose (mg)	0.125 – 0.5	0.1 – 0.4	IM is not preferred due to severe injection site pain

Table 2: Treatment dose of Digoxin in Atrial Fibrillation in Adult (Association 2014; Hindricks et al. 2021)

There are several Digoxin preparations which are available in the form of 250mcg/ml injection (2ml ampoules), 250mcg and 62.5mcg tablet and 50mcg/ml elixir (Table 3) (Clinical Pharmacy Working Committee et al. 2019).

Brand name	Characteristics	Image
Lanoxin Injection 500mcg/2ml	Manufacturer: Aspen Form: Ampoule Colour: Clear Content: A clear and colourless liquid contains 0.5mg of Digoxin in a 2ml sterile solution	

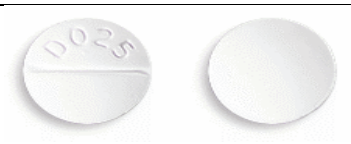
Lanoxin PG Elixir 50mcg/ml	Manufacturer: Aspen Form: Bottle (Oral liquid) Content: A clear, yellow, lime-flavoured solution containing 50mcg Digoxin BP in each 1ml of sweetened, aqueous-alcoholic vehicle	
Lanoxin PG Tab 62.5mcg	Manufacturer: Aspen Form: Round tablet Colour: Blue Content: Each tablet contains 62.5mcg of Digoxin BP	
Lanoxin Tab 250mcg	Manufacturer: Aspen Form: Round tablet Colour: White Content: Each tablet contains 250mcg of Digoxin BP	

Table 3: Type of Digoxin preparations available

7.0 Pharmacokinetic Data of Digoxin

The bioavailability (F) of Digoxin varies depending on dosage form. The highest is in intravascular injection form with 100% bioavailability followed by oral capsules, oral tablets and oral elixir with bioavailability of 90-100%, 63-75% and 75-80% respectively. In term of Volume of Distribution (Vd), it follows two-compartment model and very extensive to peripheral tissues, with a distinct distribution phase which lasts for 6-8 hours. Initially, Digoxin distributes into a small initial Vd for example in plasma and other rapidly equilibrium organ and further into other larger and more slowly equilibrium tissue such as myocardium. The average Vd of Digoxin is approximately 7.3 L/kg and can be altered by concomitant use of drugs and disease, thus subsequently may increase or reduce serum Digoxin concentration.

Age	Volume of Distribution
Adults, normal renal function	6.7 ± 1.4L/kg
Adults, renal disease	4.8 ± 1.0 L/kg
Children (1-12 years)	16.1 ± 0.8 L/kg
Infants	16.3 ± 2.1 L/kg
Neonates, full term	10 ± 1 L/kg

The metabolic clearance of Digoxin is between 0.57 to 0.86 ml/kg/min and the renal clearance is approximately equal to creatinine clearance. Some underlying disease such as chronic heart failure and concomitant use of drugs like Amiodarone, Quinidine and Verapamil may affect the Digoxin clearance. In terms of excretion, 50-70% of Digoxin is excreted unchanged by renal, primarily via glomerular filtration rate with some tubular secretion while 30-50% of the drug is excreted via non renal, primarily via biliary and intestinal tracts. Small amount is excreted through metabolism as Digoxin is a transport substrate for p-glycoprotein and its concentrations are impacted by polymorphisms and drugs that may alter p-glycoprotein activity. The half-life ($t\frac{1}{2}$) for Digoxin is

depending on age and renal function of patient as in Table 4 (Clinical Pharmacy Working Committee et al. 2019).

Age	**Half-life**
Premature neonates	61-170 hours
Full-term neonates	35-45 hours
Infants	18-25 hours
Pediatric	35 hours
Adults	38-48 hours
Adults anephric	**4-6 days**

Table 4: Half-life of Digoxin

8.0 Factors of sub- and supratherapeutic level of Digoxin

Positive inotropic effects of Digoxin were seen with low Digoxin concentration hence the lower therapeutic range (0.5-0.9 mcg/L) is used in chronic heart failure (CHF) based on the fact that most CHF patients do not demonstrate additional therapeutic benefits from higher Digoxin concentration (KF, 2002, 2005). Unlike CHF, higher concentration of Digoxin as rate control drug is needed for atrial fibrillation with therapeutic goal between 0.8-2mcg/L (Snow 2003). Considering there is some overlap between therapeutic and toxic serum Digoxin levels, symptoms of toxicity maybe reported in patients whose levels are within the therapeutic range, while others may have no symptoms when their serum Digoxin levels are above therapeutic threshold (AH et al. 1995).

Digoxin supratherapeutic or toxicity is often manifested by several clinical signs, most importantly cardiac arrhythmias that can be developed in high risk patients including those with renal insufficiency, heart failure and dehydration (KM et al. 2004). Hypoxia secondary to chronic pulmonary disease, hypokalemia, hypomagnesemia and hypercalcemia are also indicated to increase the risk of developing arrhythmias induced by Digoxin. The common non-cardiac symptoms include weakness, lethargy, anorexia, nausea and vomiting. Visual effects with altered colour perception including yellowish vision (xanthopsia) and mental status changes may occur (Parker RB. 2005). The mechanism for the increase in Digoxin toxicity risk secondary to hypokalemia derives from the fact that when K^+ is low, more K^+ binding sites are open for Digoxin binding, increasing the effective concentration of Digoxin within the heart (Rang HP. 1995).

In addition, Digoxin subtherapeutic and toxicity also may be predisposed by interactions with other concomitant drugs or comorbidities which can increase or decrease the concentration or effects of Digoxin as outlined in Table 5 and Table 6. One mechanism of drug interaction with Digoxin is change in absorption due to increased contact time in small intestine following use of anticholinergic agents together which slow gastrointestinal motility (KM et al. 2004). Furthermore, the other mechanisms believed to account for many drug interactions with Digoxin are the inhibition of P-glycoprotein located in the brush borders of the proximal tubule and inhibition of Digoxin metabolism secondary to a lack of *Eubacterium lentum* in the gastrointestinal tract which consequently leads to increase in Digoxin levels (Hirata S. 2005). In contrast, an inducer P-glycoprotein could reduce Digoxin plasma concentrations by limiting its absorption from gastrointestinal activity and by increasing the elimination of Digoxin (KM et al. 2004).

Increased Digoxin concentrations / effects	
Drugs / Diseases	**Mechanism of actions**
Beta blocker	May have additive effects on heart rate
Amiodarone, Quinidine, Verapamil	Inhibitors of P-glycoprotein efflux, hence reduce Digoxin clearance
ACE inhibitors	Decrease renal clearance
Tetracycline, Erythromycin, Clarithromycin	Interfere with Digoxin metabolism
Other CYP3A4 inhibitors	Inhibits CYP3A4 which minimally metabolized Digoxin
Hypothyroidism	Increase myocardial responsiveness to Digoxin

Table 5: Drugs and diseases that increases Digoxin concentrations / effects (Committee, 2019).

Decreased Digoxin concentrations / effects	
Drugs / Diseases	**Mechanism of actions**
Amiloride and Spironolactone	Reduce the inotropic response to Digoxin
Antacids (Magnesium / Aluminium liquid), Cholestyramine and Metoclopramide	Reduce Digoxin intestinal absorption
Levothyroxine and other thyroid hormone	Increase clearance of Digoxin
Rifampicin, Phenytoin	Inducers of P-glycoprotein efflux transporters, hence increase non-renal clearance
Pregnancy	Increase renal clearance and possible upregulation of p-glycoprotein
Hyperthyroidism	Reduce myocardial responsiveness to Digoxin, hypermetabolic and increase Digoxin clearance
Buproprion	Decrease Digoxin concentration by 60%

Table 6: Drugs and diseases that decreases Digoxin concentrations / effects (Committee, 2019)

9.0 Indications for Serum Digoxin Assessment

Therapeutic drug monitoring (TDM) is the measurement of plasma or blood concentrations of medications with specific characteristic such as narrow therapeutic index, large inter-individual variability in pharmacokinetics and concentration-dependent pharmacokinetics, where the consequences of undertreatment cannot be recognised clinically and can be serious if toxicity is suspected (AW, 2016). It is a valuable and useful tool to optimise and individualize pharmacotherapy, hence contributing to minimization of concentration-dependent adverse drug reactions and become an essential part of clinical management (Mordasinia et al. 2002). This also applies to Digoxin in view of its narrow therapeutic index property.

In 2009, the "Annual Monitoring for Patients on Persistent Medications" was added as a quality measurement in National Committee on Quality Assurance (NCQA) Healthcare Effectiveness Data and Information Set (HEDIS) Effectiveness of Care including the requirement to receive an annual assessment of serum potassium and renal function (serum creatinine or blood urea nitrogen) in all patients receiving Digoxin treatment for at least 180 days in the 12 months measurement period. At this point, TDM of Digoxin is warranted because hypokalemic and decrease in drug clearance state are known to predispose patients to digoxin toxicity. Based on 2009 NCQA report for commercial health plans, it was shown that there are 16.4% patients on persistent Digoxin treatment did not receive the recommended monitoring (Assurance, 2010). In addition, once stabilization of Serum Digoxin Concentration (SDC) maintenance dose is achieved, random SDC sampling has never been ruled out for further routine safety surveillance as predictive of toxicity or supplementation of clinical judgement (Mordasini MR. 2002).

According to American College of Cardiology (2009), SDC measurement is recommended and appropriate in following circumstances once therapeutic range has been reached; in response to a change to in a toxicity-provoking physiologic parameters such as decreased renal function; after the addition or discontinuation of an interacting drug; to assess clinical response; to assess adherence; or in the presence of clinical signs of Digoxin toxicity (Jessup M. 2009). Many factors may contribute to an accurate and meaningful drug concentrations measurement, including the correct sampling time. In general, blood sample should be withdrawn after steady state concentration has been achieved and just before the next dose administered as per Table 7 below.

After Dose Initiation	
With Loading Dose	12 – 24 hours (at least 6 hours after last dose)
Without Loading Dose	3 – 5 days
After Dose Adjustment	
Maintenance Dose	**Steady State:** a) Normal renal function: 5-7 days after dose adjustment b) End stage renal disease: 5-14 days after dose adjustment
	Oral: 30 minutes prior or just before next dose. If already taken, blood is taken at least 6 hours post dose.
	IV: 30 minutes prior or just before next dose. If already taken, blood is taken at least 4 hours post dose.

Table 7: Time to monitor serum Digoxin concentration (Committee, 2019)

10.0 Implications of Digoxin Use in Atrial Fibrillation Patient

The relationship between Digoxin use and risk of mortality is inconsistent and remain debatable. In 1997, the Digitalis Investigation Group (DIG) randomized clinical trial showed no difference in total mortality after almost 40 months follow up but there was a significant reduction in hospitalizations and cardiac mortality in heart failure patient treated with serum Digoxin concentration ≥ 1.2 ng/mL (Rekha G., et al. 1997). An analysis from the Stockholm Cohort study of Atrial Fibrillation (SCAF) reported that there is also no association of digoxin use on adjusted risk of mortality in hospitalized patients or outpatients whom is diagnosed with AF or atrial flutter (Friberg L. et al. 2010). Similar results were observed by Turakhia MP et al. (2014) during Retrospective Evaluation and Assessment of Therapies in AF (TREAT-AF) where Digoxin use was independently associated with mortality in newly diagnosed AF after propensity matching but heart failure status is not modified in this study. Most recently, clinical trial observations of digoxin use from the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial had been published and demonstrated the same result as previous study in patients with and without heart failure status (Lopes R., et al. 2018).

In contrast, (AFFIRM) study demonstrated that Digoxin was associated with significant increase in mortality after comorbidities and propensity are controlled regardless of gender and heart failure status where all causes mortality, cardiovascular mortality and arrhythmic mortality was 41% higher in AF patient with heart failure compared to 37% in those without heart failure (Whitbeck M. G., et al. 2013). Digoxin toxicity is held responsible for 0.3% of all the adverse drug events in the U.S., among which 82.1% required hospitalization due to its narrow therapeutic window (Shehab, N.et al. 2016). Furthermore, Chao T. et al (2015) compared the outcomes in AF patients receiving rate control treatments to AF patient group that not receiving any. They showed that use of Digoxin increased risk of mortality comparing beta blocker and calcium channel blocker therapy and similar results were observed in patients with and without heart failure (Chao T. et al. 2015). Another descriptive observational study demonstrated that among 171 digoxin intoxication patients treated in emergency departments (EDs), 6.4% deceased immediately and 13.4% deceased 30 days later (Caparrós, A.S.et al. 2019). In addition to that, two meta-analyses found to have same findings with previous study regarding the use of Digoxin in AF patient (Vamos M., et al. 2015; Wang Z., et al. 2015). In different setting, the end stage renal disease patient whom underwent haemodialysis treated concomitantly with Digoxin had overall increased risk of overall mortality if serum Digoxin level exceeds 0.9ng/ml (Chan K. et al 2010).

11.0 Conclusion

Monitoring digoxin levels plays a pivotal role in the effective management of atrial fibrillation (AF). Digoxin, a medication commonly used to control heart rate in AF patients, has a narrow therapeutic window, and its concentration in the bloodstream can be influenced by various factors, including age, kidney function, and drug interactions. Regular monitoring of digoxin levels allows healthcare providers to ensure that patients remain within the therapeutic range, optimizing its benefits while minimizing the risk of toxicity. By maintaining appropriate digoxin levels, clinicians can better control heart rate, alleviate symptoms, and improve the overall quality of life for individuals with AF. Thus, diligent digoxin monitoring is an essential component of AF management, contributing to safer and more effective treatment strategies for this prevalent cardiac arrhythmia.

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