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# Pharmacokinetic Changes and Dosage Adjustment of Digoxin in Elderly Patients with Atrial Fibrillation: A Narrative Review

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## Abstract

Digoxin is a cardiac glycoside medication commonly used to control rapid heart rates in Atrial Fibrillation (AF). However, digoxin has a narrow therapeutic range and can be associated with adverse effects, including increased mortality risk, especially in the elderly. Pharmacokinetic changes occur with aging, affecting the way drugs are absorbed, distributed, metabolized, and eliminated from the body. Thus, this narrative review aimed to assess the optimization of digoxin dosing in elderly patients with AF while considering pharmacokinetic changes due to aging. We performed a comprehensive computerized search of relevant English articles and a manual examination of reference lists from primary sources formed the basis of this scoping review. This involved an extensive computerized search of relevant articles in English and a manual search of the reference lists of original articles. The review highlighted the need to carefully monitor digoxin levels in elderly patients due to changes in body composition, protein binding, hepatic clearance, renal excretion, and other factors affecting drug metabolism. Furthermore, we summarized guidelines and recommendations for optimizing digoxin dosing in elderly patients with AF. By shedding light on the intricacies of optimizing digoxin dosing in the elderly with atrial AF and emphasizing the significance of accounting for age-related pharmacokinetic changes, this review offers valuable insights for healthcare practitioners and researchers in the field. Addressing these aspects is crucial to enhancing therapeutic outcomes and minimizing potential risks associated with digoxin therapy in this vulnerable patient population

**Keywords***:* digoxin, pharmacokinetics, atrial fibrillation, aged, elder

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## Introduction

Digoxin is a medication that belongs to a group of drugs known as cardiac glycosides. It is frequently employed to control rapid heart rates in Atrial Fibrillation (AF). William Withering initially brought digitalis to clinical cardiology in Birmingham in 1785. Since then, it has been frequently utilized to decrease heart rate in AF.[1,2] The most frequent type of arrhythmia seen in clinical settings.[3] Digoxin's therapeutic range is limited, and other medical conditions can substantially impact its levels.[4]

Observational studies have reported a higher risk of mortality associated with using digoxin,[5–7] which has led to decreased usage due to safety concerns.[8–10] The safety and effectiveness of digoxin can also be affected by aging. As people age, their body undergoes various physiological changes.[11,12] In addition to having altered function, older people may also react differently to medications in terms of mechanical reactions, receptor mechanisms, homeostatic alterations, and brain function.[13] As a result, drug therapy in an elderly patient is unpredictable. Thus, medication should be carefully monitored, especially with drugs with narrow therapeutic indexes such as digoxin.

Our research aimed to conduct a narrative scoping review of the existing literature on optimizing digoxin dosing in elderly patients with AF while considering the changes in pharmacokinetics that occur due to aging. To achieve this, we performed a computerized search of relevant articles written in English. We identified references of interest by searching PubMed and Google Scholar using various combinations of search terms, such as "Digoxin", "Pharmacokinetic", "Atrial Fibrillation", and "Aged", either alone or in combination. Furthermore, we manually searched the reference lists of original articles for additional relevant articles.

## Pharmacology and Mechanism of Action

Digoxin originated from the foxgloves, *Digitalis lanata*. It is a cardiotonic glycoside and belongs to the *digitalis* class. The chemical formula of digoxin is C41 H64 O14. In 1954, the FDA approved using cardiac glycosides, including digitalis and digoxin, to treat various heart problems, including atrial flutter and AF.[14] Digoxin is also widely used to manage congestive heart failure and arrhythmia[15,16] in spite of its narrow therapeutic index and potentially fatal toxicity, especially in the elderly.

The incidence and prevalence of heart failure in the elderly are relatively high, and digoxin is the most frequently prescribed in the over-65-year population.[17,18] Digoxin is usually combined with diuretic therapy to reduce heart failure symptoms and increase exercise ability.[15] In the oral route, digoxin is absorbed incompletely. The bioavailability of digoxin ranged from 50% to more than 90% of the oral dose.[19] This aspect should be carefully considered, as it directly affects the drug's concentration in the bloodstream and its efficacy at the intended site of action.

Digoxin plays a role in the different levels of heart cells. It has positive inotropic effects and negative chronotropic and dromotropic action.[20] It also increases the availability of calcium and inhibits the sodium-potassium pump (Na+ /K+ -ATPase). Consequently, an increase in the intracellular $Na^+$ concentration facilitates the entry of $Ca^{2+}$ into the cell, which increases cardiac inotropic.[21] Thus, it will shorten the cardiac action and increase calcium for the sarcomeric excitation-contraction coupling.[22] Moreover, *digitalis* compounds increase vagal efferent activity in the heart. Its parasympathomimetic action lowered the conduction velocity of electrical impulses in the atrioventricular node, thus slowing the ventricular response rate in AF.[18] (Fig.1)

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**Pharmacokinetic Changes with Aging**

Aging is shown by a progressive change in the physiological and functional capacities of the human body, a reduction in homeostatic mechanisms, and an impaired response to receptor stimulation. This might alter the pharmacokinetics of drugs, leading to clinically relevant consequences concerning safety and efficacy.[23,24] Elder people are at higher risk of experiencing adverse drug reactions due to age-related changes in how drugs are absorbed, distributed, metabolized, and eliminated from their bodies, as summarized in Table 1.[25]

The impact of pharmacokinetics on the body depends on various properties of a drug, including its pH-dependent ionization, lipid solubility, binding affinity to proteins, metabolic pathways, and renal excretion rate. Drugs undergoing significant first-pass metabolism may have higher bioavailability when impaired hepatic clearance. As people age, their body composition changes, with an increase in body fat and a decrease in both lean body mass and total body water. These changes can cause an increase in the volume of distribution for lipophilic drugs and a decrease for hydrophilic drugs.[26] The impact of drugs on the body is linked to the amount of unattached drug molecules in the blood. Therefore, modifications in how drugs attach to proteins in the blood can have considerable effects on patients. This is particularly crucial for drugs that strongly bind to proteins and require precise dosing. Although changes in protein binding that occur in older adults are often ascribed to aging, they are usually caused by accompanying medical conditions such as kidney or liver disease, as well as diabetes, that modify how drugs bind to proteins.[27]

The liver's microsomal cytochrome P450 (CYP) enzymes are essential for breaking down various drugs, with CYP3A being particularly significant due to its vast range of pharmacological substrates. Several studies indicate that the elderly population experiences decreased clearance of drugs metabolized by CYP3A.[28] One way to estimate the degree of impairment in kidney function is by measuring the level of creatinine in the blood and using it to calculate creatinine clearance. This can be done using formulas such as the Cockcroft and Gault equation.[29]

Digoxin toxicity is a frequent occurrence among older individuals and is linked to various factors such as reduced lean body mass, a decline in glomerular filtration rate (GFR), reduced muscle mass, potassium depletion

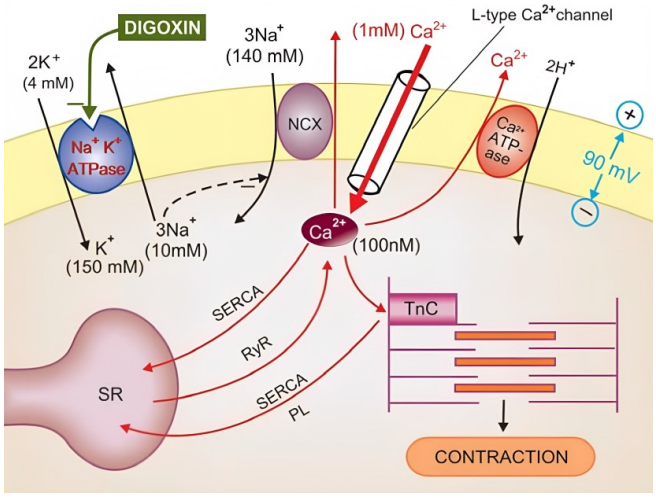


**Figure 1. Mechanism of Action of Digoxin[46]**

**Table 1. Age-related Changes that Affect Drug Pharmacokinetics[25]**

| Pharmacokinetic Parameter | Physiological Parameter | Effects in Older People compared to Younger Ones |
|---|---|---|
| Absorption | Acid secretory capacity of gastric mucosa | ↓ resulting in ↑ gastric pH and more rapid emptying of stomach |
| | Gastrointestinal blood flow | ↓ |
| | Gastrointestinal motility | ↓ |
| Bioavailability | First-pass effect | ↓ as a result of ↓ hepatic clearance |
| Distribution | Body fat | ↑ |
| | Lean body mass | ↓ |
| | Total body water | ↓ |
| | Serum albumin concentration | ↓ |
| | α1-Glycoprotein concentration | ↑ |
| Hepatic clearance | Size of the liver and hepatic blood flow | ↓ resulting in ↓ oxidation and reduction capacity |
| Renal clearance | Glomerular filtration rate | ↓ |
| | Renal plasma flow | ↓ |
| | Filtration fraction | ↑ |
| | Tubular function | ↓ resulting in ↓ reabsorptive capacity |

↑ indicates increase; ↓indicates decrease.

resulting from diuretic use, drug interactions, and the presence of other medical conditions. As the body ages, the elimination half-life of digoxin is prolonged and the volume of distribution is reduced.[30] A study of more than 1,000 nursing home residents in Canada found that 32% of elderly patients with heart failure were treated with digoxin. Of these patients, 80% received doses that exceeded recommended levels. Serum digoxin levels were higher than toxic in 30% of patients, and 26% were also taking medications known to interact with digoxin, increasing the risk of adverse effects.

**Guidelines and Recommendations**

Digoxin is recommended by the American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Rhythm Society (HRS) for heart rate control in AF with left ventricular dysfunction at a dose of 0.25 mg I.V. with repeat dosing to a maximum of 1.5 mg over 24 hours and for maintenance doses, namely oral doses of 0.125-0.25 mg once daily.[31] Similarly, the 2020 European Society of Cardiology (ESC) Guidelines, in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS), recommend the use of digoxin for heart rate reduction in AF patients. For IV formulations, the suggested dose is 0.5 mg IV bolus (0.75-1.5 mg over 24 hours in divided doses). As for maintenance therapy, oral doses of 0.0625 mg to 0.25 mg are typically prescribed once daily.[32]

Digoxin appears to minimize the risk of hospitalization in individuals with an ejection fraction (EF) of < 45% who cannot tolerate beta-blockers. For patients with a pulse rate of 70 beats per minute or higher, an alternative option is ivabradine. Additionally, patients should receive an angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin

receptor blocker (ARB), along with a mineralocorticoid receptor antagonist. During long-term therapy with digoxin, it is essential to monitor plasma digoxin levels regularly. The therapeutic dosage of digoxin is typically maintained between 0.6 to 1.2 ng/mL in the blood. However, caution should be exercised as certain medications, such as amiodarone, diltiazem, verapamil, and quinidine, can elevate digoxin levels in the bloodstream. Digoxin levels are used as a good toxicity marker but must be interpreted clinically because serum levels are not always a good indicator of toxicity.[33]

Digoxin remains a prevalent pharmacological agent in contemporary clinical practice, with frequent prescription for elderly patients. The aging process entails continuous structural and functional changes in aging populations, profoundly impacting critical organ systems. The decline in homeostatic capacity and functional reserve bears significant pharmacokinetic implications. Consequently, the elderly become more vulnerable to diseases and drug toxicity. To ensure safe and effective use of digoxin in older adults, specific recommendations include: optimizing polypharmacy by reducing the total number of drugs administered, discontinuing if deemed ineffective, taking into account potential drug-drug interactions and comorbidities, conducting regular medication reviews, implementing therapeutic drug monitoring, considering drug kinetics, and emphasizing compliance through appropriate dosage forms. These practices are vital for enhancing the clinical outcomes and well-being of elderly patients receiving digoxin therapy.[30]

**Adverse Events and Monitoring**

Aging causes changes in body condition, which, when combined with decreased kidney function and volume of distribution, prolongs digoxin elimination in plasma and increases bioavailability. Digoxin's increased pharmacodynamic sensitivity exacerbates the increased pharmacokinetic toxicity risk. The increased risk of pharmacokinetic toxicity is exacerbated by increased pharmacodynamic sensitivity to digoxin.[30] Rich et al. reported 7,788 patients in the Digitalis Investigation Group (DIG) study divided into 5 age categories: < 50 years (n = 5,841), 50 to 59 years (n = 1,545), 60 to 69 years (n = 2,885), 70 to 79 years (n = 2,092) and ≥ 80 years (n = 425) used digoxin with an average dose of 0.25 mg. The average serum digoxin level tends to be higher in older patients. Increasing age strongly predicts digoxin side effects in patients with HF.[34] Based on the study report, it was found that in elderly patients, digoxin is difficult to manage because there are many complications, and administration of digoxin to older patients increases hospitalization risk.[35,36]

Digoxin's elimination half-life is prolonged with age, and its volume of distribution is reduced.[37] Digoxin toxicity symptoms in the elderly are varied with the more common features, including anorexia, cognitive changes, hazy vision, and arrhythmia.[38–40] Moreover, the most important age-related change is decreased renal function, especially for digoxin, where poorer renal excretion requires lower doses to avoid toxicity.[41]

A previous study in a meta-analysis of 19 studies evaluated the correlation between digoxin use and mortality.[42] The Digitalis Investigation Group (DIG) study showed that serum concentrations equal to or greater than 1.2 ng/ml were correlated with a 56% increase in death risk compared to patients without taking the drug.[15] Subsequent posthoc analysis of the same DIG study indicated that digoxin treatment was considered safe when serum levels ranged from 0.5 to 0.9 ng/mL, as opposed to levels above 1.0 ng/mL.[43] Moreover,

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patients with AF using anticoagulants showed serum digoxin correlated with higher urinary excretion of thromboxane B2. In addition, in vitro experiments demonstrated that digoxin escalated platelet activation in a prestimulated stage in patients with serum digoxin levels of 1.2 ng/mL. These findings indicate the importance of maintaining digoxin levels below 1 ng/mL.[44]

Furthermore, the combination of digoxin therapy was found to elevate the risk of overall mortality in patients with end-stage renal disease on hemodialysis. As a result, guidelines have recommended that serum digoxin concentrations should ideally be maintained below 1.0 ng/mL, with a preferred range of 0.7 to 0.9 ng/mL.[45] Although current U.S. and European guidelines do not specifically recommend measuring serum digoxin levels in patients with AF, the measurement may help the monitoring to reach the goal of therapy.

**Further Directions**

Several potential areas for future research exist to optimize digoxin dosing in elderly patients with AF. These may include the development of novel biomarkers to predict better digoxin pharmacokinetics and dosing requirements, pharmacogenomic studies to identify genetic factors that influence digoxin metabolism and response, and using non-invasive monitoring techniques to monitor digoxin efficacy and toxicity. Additional randomized controlled trials may be conducted to compare the efficacy and safety of different digoxin dosing strategies and refine individualized dosing approaches.

Long-term outcomes associated with digoxin use in elderly patients with AF, such as the risk of adverse events like digoxin toxicity, hospitalization, and mortality, should also be investigated. Furthermore, researchers may explore ways to implement optimal digoxin dosing strategies in clinical practice, including interventions to improve prescriber education and adherence to evidence-based dosing recommendations.

**Conclusion**

Digoxin, a commonly used medication for controlling rapid heart rates in AF patients, encounters significant pharmacokinetic changes with age, complicating dosage adjustment for the elderly who are at higher risk of adverse reactions. To ensure safety and effectiveness, healthcare professionals should regularly monitor renal and hepatic function in elderly patients. Medication reconciliation is also crucial to identify potential drug interactions that may lead to toxicity. While current guidelines recommend a low maintenance dose for heart rate control, individualized dosing based on patients' unique clinical characteristics and response to treatment is essential. By carefully tailoring treatment and monitoring, healthcare providers can strike a balance between therapeutic benefits and risks, optimizing digoxin usage in elderly AF patients.

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**Conflit of Interest**

The authors declare no conflicts of interest.

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