The Place of Digoxin/Digitalis Cardiac Agent/Today in the Treatment of Elderly Population: The Challenges of Undefined Dose Effect Relationship and State of the Art

H. Tesfaye

Abstract—Digoxin remains one of the most commonly prescribed of all cardiac medications. The main indications for digoxin usage include atrial fibrillation and heart failure; both these conditions are more prevalent in older patients. Given the aging population and the increasing incidence of heart failure we would expect prescribing of digoxin to remain as frequent or to even increase in older patients. Older patients are also more likely to develop toxicity and diagnosis of digoxin toxicity can be difficult in this group. Numerous components contribute to the development of toxicity in older patients, ranging from aging-related changes in renal function or body mass to polypharmacy and possible interactions with digoxin. It is therefore important to understand how the pharmacokinetics of digoxin may be altered in the older population. Application of basic pharmacological principles may be helpful in anticipating these problems. This review describes the pharmacokinetics of digoxin, the changes in pharmacokinetics with increasing age and how concomitant disease states or drug interactions may affect the pharmacokinetics of digoxin. The main objectives of this paper is to draw attention to pro and contra challenging opinions on digoxin use for elderly population, where, significantly high number of patients on long term digoxin therapy is exposed to levels beyond recommended and evidently within potentially toxic levels. Emphasizing and discussing the burdens of poly pharmacy and possible drug–drug interactions and benefits of therapeutic drug monitoring (TDM) is relevant in these regards.

Keywords—Digitalis toxicity, digoxin dosage, elderly patients.

I. INTRODUCTION

In ancient times plant extracts containing cardioactive steroids we know today as cardiac glycosides (digitalis) were used either for curing or poisoning purposes. Native people of old Egypt and ancient Romans had also used digitalis as medicine against several disorders including state of oedema. Certain steroids and their glycosides found in nature (Digitalis purpurea, Digitalis lanata, and Strophantus gratus) were known to have characteristic actions on contractility and electrophysiology of the heart. Developments of digitalis from the folk remedy to the cardiac specific medicine is considered the merit of William Withering, who described digitalis in particular as medicine most likely for oedema of cardiac origin. Reportedly an old woman in Shropshire cured some people with dropsy; Withering, who heard about the herbal user assumed that the component of foxglove may be the cause of that effect. Withering thought that it acts on kidney due to its diuretic effect observed. However, he later reported its power on the heart function. While earlier empirical use of digitalis is well documented, William Withering is credited with formally introducing digitalis into clinical medicine over two centuries ago publishing a book titled “An account of digitalis (dried leaves of the purple foxglove) and some of its medical uses, where he included practical remarks on dropsy and other diseases. [1] Withering also emphasized the significant toxicity behind the cardiac glycosides extracted from Foxgloves in collection of cases he published today used as historical document. [2]. With the development of chemical techniques, digitoxin was isolated and identified from Digitalis purpurea and digoxin from Digitalis lanata. Since then, digitalis glycosides have been the subject of considerable discussion and experimentation. Introduced for the treatment of the dropsy, digoxin was soon promoted as a treatment for a wide variety of conditions, including mania and pneumonia, with considerable ill-effects. After more than two centuries in use the secret of this medicine is only gradually discovered thanks to development of science and technology as well as outcome research approach of modern medicine. Although clinical experience, experimental data and haemodynamic studies supported the use of digitalis for the treatment of heart failure, repeated controversies surrounded its efficacy and appropriate indications. At the end of the last century, the issue was not whether digoxin is effective, but whether it has a role in patients with sinus rhythm treated with ACE-inhibitors and in heart failure with preserved systolic function. [3] Although digitalis continued to be an important part of heart failure management, the role of digoxin in patients with heart failure and sinus rhythm has been increasingly challenged.

In this paper we go through development, state of the arts and place of digoxin in treatment of heart failure today. As mentioned above digoxin (digitalis) as remedy has long been used to treat heart failure; however, complete analysis of its overall effectiveness was not available until recently.
Results of the Digitalis Investigation Group trial showed that adding digoxin to standard heart failure therapy had no effect on mortality. [4] However, adding digoxin decreased hospitalizations related to heart failure and improved symptoms in patients treated for heart failure. In a prospective, randomized, double-blind, placebo-controlled multicenter trial of patients with chronic, stable mild to moderate heart failure secondary to left ventricular systolic dysfunction who had normal sinus rhythm and were receiving long-term treatment with diuretic drugs and digoxin, authors demonstrated that withdrawal of digoxin (placebo group) or its continuation (digoxin group) had significantly different outcomes. Patients withdrawn from digoxin therapy showed worsened maximal exercise capacity compared with those patients who continued to receive digoxin. Patients withdrawn from digoxin therapy showed also an increased incidence of treatment failures in digoxin withdrawal group compared to digoxin maintenance group. [5].

II. DIGOXIN VERSUS OTHER TREATMENT OPTIONS IN HEART FAILURE

ACE inhibitors, beta blockers and spironolactone have been shown to improve survival in patients with heart failure. Consequently, the role of digoxin in the treatment of heart failure remains secondary, despite renewed interest in its use. Digoxin has been shown to reduce the morbidity associated with congestive heart failure but to have no demonstrable effect on survival. In the absence of a survival benefit, the goal of digoxin therapy is to improve quality of life by reducing symptoms and preventing hospitalizations.

Some authorities declare that digoxin should be used routinely, in conjunction with diuretics, ACE inhibitors, beta blockers and spironolactone, in all patients with severe congestive heart failure and reduced systolic function. It is also advised to be added to the therapy of patients with mild to moderate congestive heart failure if they have not responded adequately to an ACE inhibitor or a beta blocker. [6], [7] If digoxin acts primarily by reducing neurohormonal activation, its value is in question in patients with heart failure who are already being treated with beta blockers. Patients with acute digoxin toxicity often present with hyperkalemia. The administration of calcium, which is often used in the treatment of hyperkalemia, has long been presumably contraindicated in the setting of digoxin toxicity. This is based on a proposed synergistic relationship between cardiac glycosides, which cause a physiologic rise in intracellular and extracellular calcium, to explain the enhanced toxicity seen with concurrent calcium administration. [8] Studies also demonstrate that high extracellular calcium increased the toxicity of cardiac glycosides at lower doses. [8], [9] Individual case reports have not demonstrated adverse effects from the administration of calcium to treat hyperkalemia in the setting of digoxin toxicity. [10], [11] A recent study examined the effects of the administration of intravenous calcium chloride in a porcine model of digoxin toxicity. Although the animals in the treatment group did not seem to develop increased toxicity, all animals developed asystole secondary to digoxin toxicity. No clear benefit or detriment related to the administration of Calciumchloride was shown. An earlier study, using a guinea-pig model of digoxin-induced hyperkalemia, reported a trend toward decreased rates of dysrhythmia and death following treatment with intravenous calcium chloride. [12] Until definitive data demonstrating the safety and efficacy of calcium administration in the setting of digoxin-induced hyperkalemia are available, its use should be avoided.

The goal of digoxin therapy in patients with congestive heart failure is to improve quality of life by reducing symptoms and preventing hospitalizations. [13] Fundamental cellular effects of dioxin is Inhibition of Na+, K+ -ATPase leading to increase of intracellular sodium and extracellular calcium. [14] Positive inotropic effect (used for congestive heart failure) Electrophysiologic action (used as antiarrhythmic) includes influences on conductivity, refractory period, and automaticity. In the DIG trial digoxin therapy was most beneficial in patients with ejection fractions of 25 percent or lower, patients with enlarged hearts (cardiothoracic ratio of greater than 0.55) and patients in NYHA functional class III or IV. [4] The findings of the DIG trial also indicated that digoxin was clinically beneficial in subgroups of patients with less severe forms of heart failure.

Using direct clinical measures of heart failure, the PROVED, and the RADIANCE trials showed definite clinical improvement in patients who were treated with digoxin, even patients with mild heart failure. [5], [15] At present, patients with preserved left ventricular systolic function probably should not be treated with digoxin. Based on the study findings, digoxin therapy may be effective in patients with mild or moderate heart failure, although the magnitude of the effect may be quite modest. [16] Reanalyses of the trial’s findings have raised new questions about the role of digoxin in heart failure treatment. These new analyses showed that low serum digoxin concentrations used in patients with more severe disease offered the most benefit. Another controversy regarding digoxin therapy is its role in the treatment of symptomatic diastolic dysfunction. The DIG ancillary trial demonstrated a trend toward decreased hospitalization and improved exercise performance in patients who received digoxin; however, these benefits were not statistically significant. [17] Diastolic heart failure treatment has been directed at modifying physiologic factors (e.g., decreasing heart rate, controlling blood pressure) because of the paucity of outcome data. [18] Pump function is relatively preserved in patients with diastolic heart failure, and inotropic therapy is usually not appropriate in this population. Clinical trials are underway to provide better guidelines for the treatment of diastolic heart failure; however, digoxin will not likely emerge as a standard therapy. [18], [19] Digoxin generally does not have a role in the treatment of diastolic heart failure and is not a first-line therapy for managing atrial fibrillation in patients with heart failure. [20] In ambulatory patients with chronic
mild to moderate diastolic heart failure and normal sinus rhythm receiving angiotensin-converting enzyme inhibitor and diuretics, digoxin had no effect on natural history end points such as mortality and all-cause or cardiovascular hospitalizations. [21].

III. DIGOXIN IN ACUTE MYOCARDIAL INFARCTION

Digoxin has been reported to have detrimental effects in myocardial infarction. [22] The drug may increase myocardial oxygen consumption by augmenting contractility and inducing peripheral or coronary vasoconstriction. It may also provoke ventricular arrhythmias and increase infarct size. [23] Because myocardial stunning may be present for weeks or longer after an infarction, digoxin therapy should be avoided in the acute phase after myocardial infarction, unless its use is strongly indicated as for conditions like atrial fibrillation, where ventricular rate control cannot be achieved with beta blockers or calcium channel blockers, or when the use of these medications is contraindicated for any reason.

Two studies in 1993 examined the effects of withdrawing digoxin therapy in patients with heart failure; The Randomized Assessment of Digoxin on Inhibitors of Angiotensin-Converting Enzyme (RADIANCE) trial and the Prospective Randomized Study of Ventricular Failure and the Efficacy of Digoxin (PROVED) trial studied patients with mild to moderate heart failure in normal sinus rhythm and showed that withdrawing digoxin in these patients significantly worsened heart failure symptoms and lowered exercise tolerance. [15], [5] Digoxin has electrophysiologic effects that decrease atrioventricular node conduction, making it potentially useful for controlling ventricular rates in patients with heart failure and concomitant atrial fibrillation. However, digoxin appears to be most effective in controlling heart rate at rest in this population. Large doses of digoxin often are required when digoxin is used alone, usually resulting in higher serum digoxin concentrations. Evidence suggests that using digoxin as a first-line agent for heart rate control may potentiate the shortening of the effective atrial refractory period, possibly facilitating short-term atrial fibrillation recurrence and increasing a patient’s risk of future episodes. [24], [25]. American Academy of Family Physicians (AAFP) and American College of Physicians (ACP) joint guidelines on managing newly detected atrial fibrillation do not apply to patients with NYHA class IV heart failure, but may be applied to patients with less severe symptoms [26]. For patients with atrial fibrillation, the AAFP/ACP guidelines recommend the following drugs as first-line therapy for controlling heart rate during exercise and while at rest: atenolol, metoprolol, diltiazem, and verapamil. Digoxin has only been shown to effectively control heart rate at rest and, therefore, should only be used as a second-line therapy for heart rate control in patients with atrial fibrillation.

Digoxin therapy may be delayed until the patient is stabilized using these agents and initiated only if the patient remains symptomatic. This recommendation is supported by findings from a meta-analysis of seven randomized trials published before the PROVED, RADIANCE, and DIG trials. [27]

The meta-analysis showed that the NNT to prevent the clinical deterioration of one patient was nine. The presence of a third heart sound, the severity and duration of heart failure, and cardiomegaly on a chest radiograph predicted the effectiveness of digoxin. Digoxin is not recommended for patients with significant sinoatrial or atrioventricular block.

The DIG investigators concluded that adding digoxin to standard heart failure therapy (i.e., ACE inhibitors plus diuretics) significantly decreased hospitalizations for worsening heart failure and improved exercise performance, whereas adding digoxin to standard therapy did not improve cardiovascular or all-cause mortality during the trial. [4] Reanalyses of the DIG trial have brought into question the safety of digoxin, including the optimal serum digoxin concentration for treating heart failure and the role of the patient’s sex in digoxin therapy.

IV. QUESTIONS AROUND SERUM DIGOXIN CONCENTRATIONS

Digoxin serum levels monitoring is aimed to optimise therapy, whereas the concentration required for optimal efficacy without risking toxicity remains not clearly defined even post DIG conclusion. The very challenging matter is that concentration/dose effect relation ship of digoxin, especially in elderly population, to whom digoxin is frequently prescribed. In our previous study ten year ago, only 29% of the subjects on long-term digoxin maintenance doses showed serum digoxin levels within published therapeutic ranges, whereas digoxin withdraw was warranted in 13% of cases due to levels showing probability to toxicity, despite absence of typical symptoms. Surprisingly 58% of the subjects had levels below 0.8 ng/mL and some undetectable. [28] Further more, elderly people are prone to toxicity due to natural changes conditioned by aging. Besides knowing underlying pathophysiology in the elderly patient population and the drug itself better, therapeutic drug monitoring with very qualified interpretation my help to better control the toxicity risk at the same time avoiding sub therapeutic levels. A widely used reference range for serum digoxin concentration is 0.8 ng per mL (1.0 nmol per L) to 2 ng per mL (2.6 nmol per L). This range was established to assess digoxin toxicity, not effectiveness [29].

Retrospective subgroup analysis of the DIG trial showed increased mortality in men who received serum digoxin concentrations of more than 1.0 ng per mL (1.3 nmol per L) and showed decreased mortality in men with serum digoxin concentrations of 0.5 ng per L (0.6 nmol per L) to 0.8 ng per mL. However, because less than one third of patients had a concentration measurement at one month, there was insufficient statistical power to determine whether digoxin use was associated with benefit or harm or had a neutral effect for women in this or any serum digoxin concentration range. [25] Reanalysis of the PROVED and RADIANCE trials indicated that patients with low serum digoxin concentrations (0.5 to 0.9
The cardiac toxicity from a digoxin overdose is related to digoxin’s effects on both the sympathetic and parasympathetic innervation of the heart. Consequently, digoxin poisoning may result in almost any type of cardiac dysrhythmia, including sinus bradycardia, atrial tachycardia, fibrillation or flutter with slow ventricular response, all degrees of AV block, junctional tachycardia, and ventricular tachycardia or fibrillation. However, rapidly conducted supraventricular tachydysrhythmias cannot occur, due to inhibition of AV nodal conduction. Bidirectional ventricular tachycardia is considered to be pathognomonic for digoxin toxicity and is caused by alterations of intraventricular conduction, junctional tachycardia with aberrant intraventricular conduction, or alternating ventricular pacemakers. However, the most commonly seen cardiac conduction abnormalities are premature ventricular contractions often the first signs of digoxin poisoning. Electrocardiographic manifestations of digoxin toxicity are due to decreased conduction accompanied by increased automaticity and a shortened repolarization interval. Electrocardiogram (ECG) findings include an increased PR interval, AV nodal block, and QT segment shortening. Scooping of the ST segment, commonly referred to as “Salvador Dali’s mustache,” may be found in patients with therapeutic digoxin levels and is due to ST segment and T-wave forces in an opposing direction to the major QRS forces. [31] Although some investigators advocate the use of serum levels to guide digoxin dosing, little evidence supports this approach.30 The serum level of digoxin may be used to assist in evaluating a patient for toxicity, but not to determine the efficacy of the drug. When digoxin was considered to be mainly an inotrope, higher dosages (greater than 0.25 mg per day) were generally used, and the incidence of toxicity was much higher. In the PROVED and RADIANCE trials, the mean digoxin dosage was 0.375 mg per day. However, a study of a subset of patients in the RADIANCE trial showed that increasing the digoxin dosage from a mean of 0.2 mg per day to 0.39 mg per day did not significantly improve heart failure symptoms, exercise time or serum norepinephrine levels. When lower dosages are used, the side effects of digoxin, especially ventricular arrhythmias, decrease. Use of lower dosages is particularly important in the elderly, because digitalis toxicity may be difficult to recognize in this patient population.32 It is generally agreed that digoxin should be given in a dosage of 0.125 to 0.25 mg per day. Dosages higher than 0.25 mg per day are probably unwarranted.

Renal function plays a major role in the pharmacokinetics of digoxin and is an important factor in determining the dosage. Medications such as quinidine, amiodarone and verapamil may increase the serum digoxin concentration. Thus, safe and effective dosing requires recognition of concomitant disease states and medications that could change digoxin pharmacokinetics, along with a recognition of digoxin toxicity symptoms. [32] New data questioning the effectiveness of digoxin for heart failure create a dilemma for physicians. Before these new data were published, digoxin was the only positive inotropic agent that had not been shown to increase mortality in patients with heart failure. This observation now must be reevaluated.

Although good evidence suggests that digoxin improves symptoms and reduces hospitalization in select patients with heart failure, recent data suggest that the use of higher serum digoxin concentrations in men and the use of digoxin at any concentration in women is associated with increased mortality.

V. DILEMMA ABOUT PATIENT’S SEX AND DIGOXIN TREATMENT OUTCOMES RELATIONSHIP

Controversy continues concerning the clinical utility of digoxin in women with heart failure. Investigation of the relationship of serum digoxin concentration and outcomes in women with heart failure through retrospective analysis of data from the DIG trial indicated a beneficial effect of digoxin on morbidity and no excess mortality in women at serum concentrations from 0.5 to 0.9 ng/ml, whereas serum concentrations > or =1.2 ng/ml seem harmful. [33] Digoxin use in women was apparently associated with increased mortality risk. This finding should be interpreted with caution, however, because it was based on retrospective data, and the cause of this phenomenon has not been fully elucidated. Prospective clinical trials are needed to determine the serum digoxin concentration that is associated with the most clinical benefit and to determine the role of digoxin therapy for women. Another retrospective analysis of the DIG trial that included participants with only systolic heart failure, examined the effects of digoxin on mortality based on the sex of patients. Overall, women in the DIG trial had a lower mortality rate than men. However, women randomized to receive digoxin had a higher mortality rate than women who received placebo. [34] The reason for this finding is unclear. Although female participants in the DIG trial were slightly older and had more comorbidities than their male counterparts, these factors are not thought to influence the effectiveness of digoxin therapy. [35] However, the instances of suspected digoxin toxicity and hospitalization were similar in men and women. [34] Although there was an inadequate number of women in the DIG trial to determine whether a specific serum digoxin concentration range was beneficial, or at least did not increase mortality, it is premature to conclude that digoxin should never be used in women. It seems reasonable to initiate digoxin therapy in women only when they are clearly symptomatic despite receiving maximal treatment with more-proven agents such as diuretics like furosemide, ACE inhibitors or angiotensin-II receptor blockers and beta blockers. Although good evidence suggests that digoxin improves symptoms and reduces hospitalization in select
patients with heart failure, recent data suggest that the use of higher serum digoxin concentrations in men and the use of digoxin at any concentration in women may be associated with increased mortality, but this should be examined carefully.

Appropriate patient population and existing guidelines to prescribe digoxin

The ACC/AHA staging system for heart failure can be a useful tool when determining whether to initiate digoxin therapy. This staging system and corresponding NYHA functional classifications for heart failure are included in the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and 2009 Focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation. [36]

Whatever, digoxin therapy is used to treat heart failure patients since more than 200 years todate. However, absence of effect on overall mortality found in the DIG study associated with frequent adverse effects due to overdosing in elderly patients with impaired renal function finally persuaded medical opinion to the weak interest of digoxin in chronic heart failure. Yet, regarding strict data from the literature, it remains a lot of positive factors in favor of the interest for digoxin: reduction of morbidity, reduction of mortality at low serum concentration <1.0 ng/ml, very low cost with favorable cost-effectiveness ratio. [37]

Due age related polymorbidity, the elderly population requires treatment with multiple types of medications including cardiovascular pharmacotherapeutic regimen, where the risk versus the benefit of each medication must be strongly considered particularly because adverse effects are more often prevalent and pronounced in this population. Over the years, it has been documented that digoxin is a frequently prescribed medication in elderly populations. Although this drug can be beneficial when used in the appropriate setting, recent data would suggest that inappropriate administration of digoxin is common and not without potentially serious consequences. Currently, the use of digoxin can be advocated to control heart failure in atrial fibrillation and when added to ACE inhibitors and diuretics in those patients with symptomatic heart failure related to systolic left ventricular dysfunction. It is likely that the excessive use of digoxin in elderly populations as discussed in this review is perhaps based on the prevalence of diastolic heart failure in the elderly as well as other co-morbid conditions that may mimic heart failure signs and symptoms.

Since the elderly appear to be at high risk for digoxin toxicity, the inappropriate use of this medication to treat these conditions could result in significant and unnecessary morbidity. [40] Since the elderly appear to be at high risk for digoxin toxicity, the inappropriate use of this medication to treat these conditions could result in significant and unnecessary morbidity. To add to the challenge, older patients are also more likely to develop toxicity and diagnosis of digoxin toxicity can be difficult in this group. Despite all digoxin continues to be an important drug in long-term heart failure patient management in elderly patients. Thus, greater knowledge about the causes and prevention of digoxin toxicity should further reduce the morbidity and mortality arising from digoxin toxicity, especially in the elderly population. [41]

Digitalis glycosides have been used for more than 200 years in the treatment of heart failure, but the serum dioxin concentration required for optimal clinical efficacy and acceptable toxicity remains controversial. The study sought to determine whether there was a relationship between serum digoxin concentration, including concentrations typically regarded as low, and clinical efficacy related to digoxin in patients with symptomatic left ventricular dysfunction utilized data from two randomized, double-blinded, placebo-controlled, digoxin-withdrawal trials concluded that patients in the low serum dioxin category were significantly less likely than placebo patients to experience worsening heart failure during follow-up, but the beneficial effects of digoxin on common clinical end points in patients with heart failure were similar, regardless of serum digoxin concentration. [42]

Among cardiovascular agents, digoxin is one of the most
commonly involved in fatalities causing 17% of the reported fatalities. [43] Assessment of variations in serum digoxin concentration and their association with mortality and hospitalization in patients with heart failure demonstrated that higher serum digoxin concentrations were associated with increased mortality suggesting that the effectiveness of digoxin therapy in men with heart failure and a left ventricular ejection fraction of 45% or less may be optimized in the range of 0.5 to 0.8 ng/mL. [25] Digoxin at low serum concentration significantly reduced mortality and hospitalizations in ambulatory chronic systolic and diastolic HF patients. [44] Digoxin-associated risk in mortality may be due to an increases in myocardial oxygen consumption and arrhythmogenesis at higher serum concentrations. We hypothesized that the serum concentration of digoxin is a major determinant factor of its efficacy on mortality rates in patients with congestive heart failure. The maintenance of digoxin's serum concentration at the lower end of the reference range, i.e., between 0.5 and 0.8 ng/mL may reduce mortality rates as well as improve clinical symptoms. [45] Clinical studies have solidified the utility of digoxin in patients with left ventricular dysfunction and normal sinus rhythm. No definitive data have been published to clarify the range of serum digoxin concentrations associated with clinical benefit. The traditional therapeutic range of 0.8-2.0 ng/ml was developed originally to classify digoxin toxicity, not efficacy. In addition, this reference range was used before publication of the Digitalis Investigators Group trial. Clinical and neurohormonal studies have attempted to characterize serum concentrations that are associated with clinical efficacy. [46] Post hoc analyses of the Digitalis Investigation Group (DIG) trial indicate that digoxin at low (0.5 to 0.9 ng/ml) serum digoxin concentration reduces mortality, which is eliminated at higher (> = 1 ng/ml), and that low-dose digoxin (< = 0.125 mg/day) predicts low serum concentration. The median dose of digoxin (0.25 mg/day) and the target concentration (0.8 to 2.5 ng/ml) were higher than what are currently recommended, which in part may explain the lack of long-term mortality benefit of digoxin in the DIG trial. Ahmed et al. examined the effect of digoxin on short-term outcomes; 1-year all-cause mortality occurrence and concluded that dinoxin reduced 1-year mortality and hospitalization in patients with chronic heart failure receiving angiotensin-converting enzyme inhibitors and diuretics, however suggesting that randomized clinical trials are needed to determine the effect of low-dose digoxin in contemporary patients with chronic heart failure. [47].

Digoxin at low SDC was associated with a reduction in mortality and hospitalization in chronic geriatric HF, and low-dose digoxin was the strongest predator of low serum digoxin concentration.[48] Digoxin at serum concentration 0.5-0.9 ng/mL reduces mortality and hospitalizations in all heart failure patients, including those with preserved systolic function. At higher serum concentration, digoxin reduces HF hospitalization but has no effect on mortality or all-cause hospitalizations. [49] Consensus guidelines by the Heart Failure Society of America and the American College of Cardiology/American Heart Association recommends that the lower dose should be used in patients over 70 years of age, those with impaired renal function, or those with a low lean body mass, whereas digoxin toxicity is commonly associated with serum levels >2 ng/ml but may occur with lower digoxin levels if hypokalemia, hypomagnesemia, or hypothyroidism coexist. Likewise, the concomitant use of agents such as quinidine, verapamil, spironolactone, flecainide, and amiodarone can increase serum digoxin levels and increase the likelihood of digoxin toxicity. Digoxin concentrations increased during concomitant administration of clarithromycin, where the percentage increase in digoxin concentrations after the usual oral dose of clarithromycin was approximately 70% was also reported. [50] For patients with heart failure and atrial fibrillation with a rapid ventricular response, the administration of high doses of digoxin (>0.25 mg daily) for the purpose of rate control is not recommended. When necessary, additional rate control should be achieved by the addition of beta-blocker therapy or amiodarone (strength of evidence = C). If amiodarone is added, the dose of digoxin should be reduced. Digitalis preparations are now entering their fourth century of clinical use for the treatment of chronic heart failure symptoms. Its clinical efficacy can no longer be doubted and its safety has been verified by the multicenter DIG trial. Future advances in pharmacogenetics should facilitate identification of those patients most likely to benefit from its pharmacologic effects. [51] Digoxin at low SDC significantly reduced mortality and hospitalizations in ambulatory chronic systolic and diastolic HF patients. [52] Most heart failure patients are > or = 65 years, yet the effects of digoxin on outcomes in these patients have not been well studied. Low-dose digoxin (< or = 0.125 mg/d) was the strongest independent predictor of low SDC and digoxin at low SDC was associated with a reduction in mortality and hospitalization in chronic geriatric HF, and low-dose digoxin was the strongest predictor of low serum concentration. [48]

VI. CONCLUSIONS

Based on existing evidence some patients still benefit from digoxin. Most of the patients on chronic use of digoxin are elders. According to objective reports many elderly patients live with toxic levels of digoxin most probably for long time, before being discovered. Given that the age determined organ function deterioration as well as increased sensitivity of elderly patients to toxicity warrant special attention to this patient population if they are on digitalis. It is important to understand how the pharmacokinetics of digoxin may be altered in the older population, so that the specific geriatric pharmacology of the drug must be considered, when digoxin is used in elderly patients. Clinical benefit should also be documented before proceeding to long-term maintenance therapy. In selected elderly patients, withdrawal of digoxin with careful follow-up may be a worthwhile procedure. Nevertheless indication should also be limited to conditions, where other alternatives
fail to achieve control of the disease.

REFERENCES


