



Department of Vermont Health Access

Therapeutic Class Review Cardiotonic Agents

Overview/Summary

Digitalis was initially obtained from the foxglove plant, *Digitalis lanata*, and later found to possess positive inotropic effects on the heart.¹ Digoxin, is one of the cardiac glycosides and is extracted from the leaves of the *Digitalis lanata* plant.² The efficacy of digoxin in patients with heart failure and atrial fibrillation has been well established and widely accepted. Digoxin is a potent and selective inhibitor of the active transport of Na⁺ and K⁺ across the cell membrane.¹ In congestive heart failure, digoxin increases cardiac contractility by inhibiting the Na⁺ and K⁺ adenosine triphosphate pump. In supraventricular arrhythmias, digoxin suppresses atrioventricular node conduction of electrical impulses thereby slowing ventricular rates.³ Adverse effects and drug interactions are common with digoxin and its narrow therapeutic concentration range makes precise dosing extremely vital in order to limit toxicity.

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade Name)	Medication Class	Generic Availability
Digoxin (Lanoxin [®] , Lanoxin Pediatric [®])	Cardiotonic agents	✓

Indications

Table 2. Food and Drug Administration (FDA) Approved Indications²

Indication	Digoxin
Treatment of mild to moderate heart failure	✓
Control of ventricular response rate in patients with chronic atrial fibrillation	✓

Pharmacokinetics

Table 3. Pharmacokinetics^{2,3}

Digoxin Dosage Form	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Elimination	Serum Half-Life*
Injection	100	25	16 metabolized via hydrolysis, oxidation and conjugation	Renal	1.5 to 2.0 days [†]
Pediatric elixir	75 to 85				
Tablet	60 to 80				

*Renal excretion of digoxin is proportional to glomerular filtration rate.

†In normal renal function. Half-life may range from 3.5 to 5.0 days in anuric patients.

Clinical Trials

In a cohort study comparing patients with atrial fibrillation (AF), congestive heart failure (CHF) or both, one year mortality was evaluated. Those patients with AF or CHF receiving digoxin did significantly worse than those patients not receiving digoxin. However, there was no difference in mortality in patients with AF and CHF between the groups.⁴ When digoxin was combined with other agents (carvedilol, diltiazem or betaxolol), there was a significant reduction in ventricular rate.^{5,6} Additionally, when compared to other agents (carvedilol or verapamil), there was no significant difference in primary outcomes.^{5,7} The trial by the digoxin investigator group (DIG) compared digoxin to placebo in patients with heart failure and left ventricular ejection fraction (LVEF) ≤45% receiving background CHF therapies. There was no

significant difference in mortality, mortality from cardiovascular causes or death from worsening heart failure. However, hospitalizations for worsening of heart failure and overall hospitalizations were significantly less with digoxin compared to placebo.⁸ There was also an ancillary trial conducted in parallel with the primary DIG trial. In patients with LVEF > 45%, there was no significant differences in the heart failure hospitalizations or heart failure mortality between digoxin and placebo.⁹

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Atrial Fibrillation				
<p>Hallberg et al⁴</p> <p>AF group: Patients with AF on digoxin</p> <p>vs</p> <p>patients with AF not on digoxin</p> <p>CHF group: patients with CHF on digoxin</p> <p>vs</p> <p>patients with CHF not on digoxin</p> <p>AF and CHF group: patients with AF and CHF on digoxin</p> <p>vs</p> <p>patients with AF and CHF not on digoxin</p>	<p>Cohort</p> <p>AF group: ECG finding of AF at admission, at discharge or had a discharge diagnosis of AF</p> <p>CHF group: History of CHF, a diagnosis of CHF at discharge or pulmonary edema on admission</p> <p>AF and CHF group: ECG finding of AF on admission, ECG finding of AF at discharge or a discharge diagnosis of AF, and a medical history of CHF, a diagnosis of CHF at discharge or pulmonary edema on admission</p>	<p>N=60,764</p> <p>1 year</p>	<p>Primary: One year mortality</p> <p>Secondary: Effects on LVEF, serum creatinine and acute MI</p>	<p>Primary: Patients with AF who received digoxin did significantly worse than those AF patients who did not receive digoxin (RR of death, 1.42; 95% CI, 1.29 to 1.56; <i>P</i> value was not reported).</p> <p>Patients with CHF who received digoxin did significantly worse than those CHF patients who did not receive digoxin (RR of death, 1.11; 95% CI, 1.04 to 1.19; <i>P</i> value was not reported).</p> <p>In the group of patients with AF and CHF, there was no mortality difference between those that received digoxin and those that did not receive digoxin (RR of death, 1.00; 95% CI, 0.94 to 1.06; <i>P</i> value not reported).</p> <p>Secondary: In patients with LVEF ≤30%, there was not a significant difference in rate of death between patients who received digoxin and those that did not receive digoxin (RR of death, 1.06; 95% CI, 0.86 to 1.31; <i>P</i> value not reported).</p> <p>In patients with LVEF >30%, there was not a significant difference in rate of death between patients who received digoxin and those that did not receive digoxin (RR of death, 1.14; 95% CI, 0.98 to 1.32; <i>P</i> value not reported).</p> <p>Regardless of level of serum creatinine (low, normal, high), there was not a significant difference in mortality between those who received digoxin and those who did not receive digoxin (low serum creatinine: RR of death, 1.23; 95% CI, 0.91 to 1.66; normal serum creatinine: RR of death, 1.22; 95% CI, 0.94 to 1.58; high serum creatinine: RR of death, 0.98; 95% CI, 0.83 to 1.16, respectively; <i>P</i> values not reported).</p> <p>In patients with an acute MI, the RR for death was 1.17 (95% CI, 1.10 to 1.24) between those that received digoxin and those that did not receive digoxin; <i>P</i> value was not reported.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>In patients without an acute MI, the RR for death was 1.10 (95% CI, 1.04 to 1.16) comparing those that received digoxin and those that did not receive digoxin; <i>P</i> values not reported.</p>
<p>Khand et al⁶</p> <p>Phase 1: Digoxin with placebo</p> <p>vs</p> <p>digoxin with carvedilol</p> <p>Phase 2: digoxin</p> <p>vs</p> <p>carvedilol</p>	<p>DB, PC, PG, RCT</p> <p>Patients with persistent AF for >1 month and heart failure who were receiving digoxin and diuretics</p>	<p>N=47</p> <p>Phase 1: 4 months</p> <p>Phase 2: 6 months</p>	<p>Primary: Assessment of LVEF, ventricular rate control, symptom improvement, exercise test</p> <p>Secondary: Not reported</p>	<p>Primary: Phase 1: The patients in the digoxin with carvedilol group experienced a reduction in mean ventricular rate compared to the patients in the digoxin with placebo group (65.2±15.0 vs 74.9±11.2 respectively; <i>P</i><0.0001).</p> <p>The patients in the digoxin with carvedilol group experienced improved LVEF compared to the patients in the digoxin with placebo group (30.0±9.6 vs 26.0±12.4 respectively; <i>P</i>=0.048).</p> <p>The patients in the digoxin with carvedilol group experienced an improvement in symptom scores compared to the patients in the digoxin with placebo group (seven [three to 12.5] vs eight [three to 15] respectively; <i>P</i>=0.039).</p> <p>The patients in the digoxin with carvedilol group experienced a reduced ventricular rate at rest and throughout steady-state exercise (peak ventricular rate, 106 bpm) compared to those patients in the digoxin with placebo group (peak ventricular rate, 123 bpm; <i>P</i><0.05).</p> <p>Phase 2: There was no significant difference in ventricular rate control between the digoxin and the carvedilol treatment groups (88.8±18.7 vs 75.7±10.6, respectively; <i>P</i>=0.13).</p> <p>There was no significant difference in LVEF between the digoxin and the carvedilol treatment groups (21.6±11.0 vs 27.2±11.7, respectively; <i>P</i>=0.15).</p> <p>There was no significant difference in symptom scores between the digoxin and the carvedilol treatment groups (six [two to 17] vs eight [five to 15.5] respectively; <i>P</i>=0.08).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>There was no significant difference in ventricular rate at steady-state exercise between the digoxin and the carvedilol treatment groups (<i>P</i> value not reported).</p> <p>Secondary: Not reported</p>
<p>Koh et al⁶</p> <p>Digoxin 0.125 to 0.5 mg Daily plus diltiazem 90 mg BID</p> <p>vs</p> <p>digoxin 0.125 to 0.5 mg Daily plus betaxolol Daily</p>	<p>PRO, RCT, XO</p> <p>Patients with persistent AF for >1 month</p>	<p>N=37</p> <p>7 months</p>	<p>Primary: Effects on ventricular rate, blood pressure, rate-pressure, maximal exercise tolerance</p> <p>Secondary: Safety</p>	<p>Primary: Patients in the digoxin plus betaxolol group experienced a significant reduction in ventricular rates both at rest and during exercise (67±3 and 135±5 bpm, respectively) compared to the patients in the digoxin plus diltiazem group (80±7 and 154±5 bpm, respectively; <i>P</i><0.05).</p> <p>Patients in the digoxin plus betaxolol group experienced a significant reduction in systolic blood pressure during maximal exercise (164±4 mm Hg) but not at rest (127±3 mm Hg) compared to the patients in the digoxin plus diltiazem group (173±4 and 130±4 mm Hg, respectively; <i>P</i><0.05, <i>P</i>>0.05, respectively).</p> <p>Patients in the digoxin plus betaxolol group experienced significantly less rate-pressure products at rest (85±4x102 mm Hg/min) and during exercise (213±12x102 mm Hg/min) compared to the patients in the in digoxin plus diltiazem group (105±6 and 269±12, respectively; <i>P</i><0.05 for both).</p> <p>Both the digoxin plus betaxolol group and the digoxin plus diltiazem group experienced a significant improvement in exercise capacity compared to baseline (<i>P</i><0.05), but the groups were not statistically significant from one another (9.3±0.5 vs 9.7±0.5 mean exercise tolerance; <i>P</i>>0.05).</p> <p>There were no statistical differences between the treatment groups in any of the efficacy points measured between time points at weeks four and seven months (<i>P</i> values not reported).</p> <p>Secondary: No patients withdrew from the study in either treatment group due to</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				side effects. The digoxin plus betaxolol group experienced more side effects, which were considered minimal, compared to the digoxin plus diltiazem group (<i>P</i> values not reported). The minimal side effects observed in the digoxin plus betaxolol group included dyspnea, gastric pain, fatigue and constipation.
<p>Hemels et al'</p> <p>Group 1: Digoxin 0.125 to 0.25 mg Daily plus acute (within 24 hours) ECV</p> <p>vs</p> <p>digoxin 0.125 to 0.25 mg Daily plus routine ECV</p> <p>Group 2: verapamil 120 to 360 mg Daily with acute (within 24 hours) ECV</p> <p>vs</p> <p>verapamil 120 to 360 mg Daily plus routine ECV</p> <p>Study medications were dosed to reach a target heart rate <100 bpm and were administered for 4 weeks before ECV and continued during total follow-up.</p> <p>ECV was done one month after randomization and was only performed if anticoagulation therapy had been adequate (goal INR 2.5 to 3.5).</p>	<p>MC, PRO, RCT</p> <p>Patients with persistent AF, (defined as non-self-terminating arrhythmia and requiring ECV to obtain sinus rhythm), and no contraindications to anticoagulation therapy</p>	<p>N=144</p> <p>18 months</p>	<p>Primary: Freedom from permanent AF</p> <p>Secondary: Quality of life</p>	<p>Primary: At the end of the 18 month follow-up period, there was not a statistically significant difference in patients with permanent AF between the acute and routine ECV groups (32%; 95% CI, 22 to 44 vs 31%; 95% CI, 21 to 44, respectively; <i>P</i>=0.85), despite more ECVs in the acute vs the routine group ([median three vs two ECVs; <i>P</i><0.05] and [≥3 ECVs in 54 vs 33% of patients, respectively; <i>P</i><0.01]).</p> <p>At the end of the 18 month follow-up period, there was not a statistically significant difference in patients with permanent AF between the verapamil and digoxin groups (28%; 95% CI, 19 to 40 vs 36%; 95% CI, 25 to 48, respectively; <i>P</i>=0.33), despite more ECVs in the digoxin group compared to the verapamil group ([median three vs two ECVs, respectively; <i>P</i><0.001] and [≥3 ECVs in 60 vs 28% of patients, respectively; <i>P</i><0.001]).</p> <p>Secondary: At the end of the 18 month follow-up period, there were no significant differences in quality of life between the acute and the routine cardioversion groups. Also, at the end of the 18 months, there were no significant differences in quality of life between the digoxin and verapamil groups (<i>P</i> values not reported).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Wyse et al¹⁰</p> <p>Rhythm control therapy: amiodarone, disopyramide, flecainide, moricizine*, procainamide, propafenone, quinidine, sotalol, dofetilide and combinations of these drugs (doses not specified and adjusted to maintain normal sinus rhythm)</p> <p>vs</p> <p>rate control therapy: β-blockers, calcium-channel blockers, digoxin and combinations of these drugs (doses not specified and adjusted to maintain normal sinus rhythm)</p>	<p>MC, RCT</p> <p>Patients ≥ 65 years of age who had AF that was likely recurrent, AF was likely to cause illness or death, long-term treatment for AF was warranted, no contraindication to anticoagulation therapy, eligible to undergo trials of at least two drugs in both treatment strategies and treatment with either strategy could be initiated immediately after randomization</p>	<p>N=4,060</p> <p>3.5 years</p>	<p>Primary: Overall mortality</p> <p>Secondary: Composite death, disabling stroke, disabling anoxic encephalopathy, major bleeding and cardiac arrest</p>	<p>Primary: The difference in mortality between the two groups was not significant (HR, 1.15; 95% CI, 0.99 to 1.34; $P=0.08$).</p> <p>Secondary: The rates of the composite end point of death, disabling stroke, disabling anoxic encephalopathy, major bleeding or cardiac arrest were also similar in the two groups ($P=0.33$).</p>
<p>Van Gelder et al¹¹</p> <p>Rhythm control therapy: electrical cardioversion, then sotalol 160 to 320 mg (based on weight and renal function); if recurrence within 6 months, repeat electrical cardioversion, then flecainide 200 to 300 mg daily or propafenone 450 to 900 mg daily; if recurrence again, electrical cardioversion repeated along with amiodarone 600 mg daily for 4 weeks then 200</p>	<p>MC, RCT</p> <p>Patients with recurrent persistent AF or atrial flutter, who have undergone one electrical cardioversion during the previous two years, with a maximum of two</p>	<p>N=522</p> <p>2 years</p>	<p>Primary: Composite of death from cardiovascular causes, heart failure, thromboembolic complications, bleeding, the need for implantation of a pacemaker or severe adverse</p>	<p>Primary: The composite end point occurred in 44 (17.2%) patients receiving rate-control and in 60 (22.6%) patients receiving rhythm-control (absolute difference, -5.4; 90% CI, -11.0 to 0.4).</p> <p>Death from cardiovascular causes occurred in 18 (7.0%) patients receiving rate-control and in 18 (6.8%) patients receiving rhythm-control (absolute difference, 0.2; 90% CI, -3.4 to 3.9).</p> <p>Heart failure occurred in nine (3.5%) patients receiving rate-control and in 12 (4.5%) patients receiving rhythm-control (absolute difference, -1.0; 90% CI, -3.8 to 1.8).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>mg daily</p> <p>vs</p> <p>rate control therapy: digitalis, non-dihydropyridine calcium channel blocker and β-blocker, alone or in combination</p>			<p>effects of antiarrhythmic drugs</p> <p>Secondary: Not reported</p>	<p>Thromboembolic complications occurred in 14 (5.5%) patients receiving rate-control and in 21 (7.9%) patients receiving rhythm-control (absolute difference, -2.4; 90% CI, -6.0 to 1.2).</p> <p>Bleeding occurred in 12 (4.7%) patients receiving rate-control and in nine (3.4%) patients receiving rhythm-control (absolute difference, 1.3; 90% CI, -1.5 to 4.1).</p> <p>Severe adverse effects of antiarrhythmic drugs occurred in two (0.8%) patients receiving rate-control and in 12 (4.5%) patients receiving rhythm-control (absolute difference, -3.7; 90% CI, -6.0 to -1.4).</p> <p>A pacemaker was implanted in three (1.2%) patients receiving rate-control and in eight (3.0%) patients receiving rhythm-control (absolute difference, -1.8; 90% CI, -3.9 to 0.2).</p> <p>Secondary: Not reported</p>
<p>Opolski et al¹²</p> <p>Rhythm control therapy: propafenone 450 to 600 mg/day, disopyramide 300 to 600 mg/day or sotalolol 160 to 320 mg/day</p> <p>vs</p> <p>rate control therapy: β-blockers, non-dihydropyridine calcium channel blockers, digoxin or a combination of these drugs</p> <p>All patients underwent electric cardioversion prior to the initiation of trial medication.</p> <p>Drug given to patient was</p>	<p>MC, OL, RCT</p> <p>Patients 50 to 75 years of age with AF known to be present continuously for between 7 days and 2 years with acceptable etiology of the arrhythmia related to ischemic heart disease, arterial hypertension, hemodynamically insignificant valvular heart</p>	<p>N=205</p> <p>1 year</p>	<p>Primary: Composite of death from any cause (thromboembolic complications and intracranial or other major hemorrhage)</p> <p>Secondary: Rate control, sinus rhythm maintenance, discontinuation of therapy (proarrhythmic effects), hemorrhage,</p>	<p>Primary: There was not a significant difference in composite of death from any cause between patients receiving rate control and rhythm control (OR, 1.98; 95% CI, 0.28 to 22.3; $P>0.71$).</p> <p>Secondary: Patients receiving rhythm control had a significantly lower mean heart rate (79.1 ± 8.6 bpm) in 24 hour Holter monitoring compared to patients receiving rate control (85.8 ± 7.5 bpm; $P<0.003$).</p> <p>Four patients receiving rhythm control experienced proarrhythmic effects (P value not reported). Whether this lead to discontinuation of therapy was not mentioned.</p> <p>At the end of the trial, 66 patients (63.5%) receiving rhythm control were in sinus rhythm, with 27 of these patients successfully maintained with the first antiarrhythmic compound administered after the first cardioversion (P values not reported).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>determined by their arrhythmia etiology, concomitant heart diseases and age.</p> <p>If patient had recurrent AF, cardioversion was repeated and an alternate antiarrhythmic agent was given in addition to amiodarone.</p>	<p>disease or lack of assessable etiology</p>		<p>hospitalization, new or worsening CHF, changes in exercise tolerance</p>	<p>There was not a significant difference seen in bleeding complications between the rhythm control group (eight patients) and rate control group (five patients; <i>P</i> value not reported).</p> <p>A significantly lower number of hospitalizations were seen with rate control compared to rhythm control (12 vs 74%, respectively; <i>P</i><0.001).</p> <p>Both rhythm control and rate control had significant improvements in CHF class at some point during follow up compared to baseline (<i>P</i><0.001 and <i>P</i><0.05, respectively). No difference in NYHA functional class between patients initially randomized to the two strategies was found at the end of the follow up period (<i>P</i> value not reported).</p> <p>At the end of the trial, both maximal workload and exercise duration were higher with rhythm control compared to rate control (<i>P</i><0.001 and <i>P</i><0.001, respectively).</p>
Heart Failure				
<p>Koh et al¹³</p> <p>Without digoxin, diltiazem, or betaxolol (Group I)</p> <p>vs</p> <p>digoxin 0.125 to 0.5 mg Daily (Group II)</p> <p>vs</p> <p>digoxin 0.125 to 0.5 mg Daily and diltiazem 90 mg BID (Group III)</p> <p>vs</p> <p>digoxin 0.125 to 0.5 mg Daily and betaxolol 20 mg Daily (Group IV)</p>	<p>PRO, RCT</p> <p>Patients with chronic heart failure for >1 month</p>	<p>N=45</p> <p>4 weeks</p>	<p>Primary: Heart rate, blood pressure, rate-pressure</p> <p>Secondary: Not reported</p>	<p>Primary: Resting ventricular rates were lower in all patients receiving active treatment (groups II, III, IV) compared those patients in group I who did not receive digoxin (<i>P</i><0.01).</p> <p>Ventricular rates during exercise were lower in groups III and IV compared to groups I and II (<i>P</i><0.01).</p> <p>No significant differences in ventricular rate were noted between groups III and IV, either at rest or during exercise (<i>P</i><0.01).</p> <p>Systolic blood pressure was not significantly different between the four groups (<i>P</i>=0.09).</p> <p>Rate-pressure product at rest and during exercise was significantly lower in groups III and IV compared to groups I and II (<i>P</i><0.01).</p> <p>Secondary: Not reported</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>DIG⁸</p> <p>Digoxin 0.125 to 0.5 mg Daily</p> <p>vs</p> <p>placebo Daily</p> <p>Patients continued on their other CHF therapies (including diuretics and ACE inhibitors).</p> <p>Initial dosing of digoxin was based on patient's age, sex, weight and renal function.</p>	<p>DB, MC, PC, RCT</p> <p>Patients ≥21 years of age with heart failure and LVEF of 0.45 or less and who were in normal sinus rhythm</p>	<p>N=6,800</p> <p>37 months</p>	<p>Primary: Mortality</p> <p>Secondary: Mortality from cardiovascular causes, death from worsening heart failure, hospitalization for worsening heart failure, and hospitalization for other causes (specifically due to digoxin toxicity)</p>	<p>Primary: In the digoxin group, there were 1,181 (34.8%) deaths compared to 1,194 (35.1%) deaths in the placebo group (RR, 0.99; 95% CI, 0.91 to 1.07; <i>P</i>=0.80).</p> <p>Secondary: In the digoxin group, 1,016 (29.9%) patients died from cardiovascular causes compared to 1,004 (29.5%) patients in the placebo group (RR, 1.01; 95% CI, 0.93 to 1.10; <i>P</i>=0.78).</p> <p>There were 394 deaths in the digoxin group that were attributed to worsening heart failure compared to 449 deaths in the placebo group (RR, 0.88; 95% CI, 0.77 to 1.01; <i>P</i>=0.06).</p> <p>In the digoxin group, 910 patients were hospitalized for worsening heart failure compared to 1,180 patients in the placebo group (RR, 0.72; 95% CI, 0.66 to 0.79; <i>P</i><0.001).</p> <p>Overall, the placebo group had a significantly higher number of patients hospitalized compared to the digoxin group, 2,184 vs 2,282 respectively (RR, 0.92; 95% CI, 0.87 to 0.98; <i>P</i><0.006). Other reasons for hospitalizations included cardiac events and respiratory infection.</p> <p>There was a statistically significantly higher number of patients in the digoxin group hospitalized for suspected digoxin toxicity compared to patients in the placebo group, 67 vs 31 respectively (RR, 2.17; 95% CI, 1.42 to 3.32; <i>P</i><0.001).</p>
<p>Ahmed et al⁹</p> <p>Digoxin 0.125 to 0.5 mg Daily</p> <p>vs</p> <p>placebo Daily</p> <p>Patients continued on their other CHF therapies (including diuretics</p>	<p>MC, PC, RCT</p> <p>Patients with diastolic heart failure (LVEF >45%) and normal sinus rhythm at baseline</p> <p>This was an</p>	<p>N=988</p> <p>37 months</p>	<p>Primary: Combined end point of heart failure hospitalization or heart failure mortality</p> <p>Secondary: Not prespecified,</p>	<p>Primary: At the end of the study, there was not a statistically significant difference in the number of patients who experienced heart failure hospitalization or heart failure mortality between the digoxin group and the placebo group (102 [21%] vs 119 [24%], respectively; HR, 0.82; 95% CI, 0.63 to 1.07; <i>P</i>=0.136).</p> <p>Secondary: At the end of the study, there was not a statistically significant difference in the number of all-cause deaths between the digoxin</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>and ACE inhibitors).</p> <p>Initial dosing of digoxin was based on patient's age, sex, weight and renal function.</p>	<p>ancillary trial conducted in parallel with the main DIG trial.⁸</p>		<p>however the following outcomes were studied: all-cause and cardiovascular mortality, all-cause and cardiovascular hospitalizations, and the combined outcome of heart failure hospitalization and cardiovascular mortality</p>	<p>group and the placebo group (115 [23%] vs 116 [23%], respectively; HR, 0.99; 95% CI, 0.76 to 1.28; <i>P</i>=0.925). Also, the difference in the number of cardiovascular deaths was not significantly different between the digoxin and the placebo groups (81 patients in each group; HR, 1.00; 95% CI, 0.73 to 1.36; <i>P</i>=0.978).</p> <p>At the end of the study, there was not a statistically significant difference in the number of all-cause hospitalizations between the digoxin group and the placebo group (68 vs 67%, respectively; HR, 1.03; 95% CI, 0.89 to 1.20; <i>P</i>=0.683). Also, the difference in the number of cardiovascular hospitalizations was not significantly different between the digoxin and the placebo groups (241 [49%] vs 225 [45%], respectively; HR, 1.10; 95% CI, 0.92 to 1.32; <i>P</i>=0.301).</p> <p>At the end of the study, there was not a statistically significant difference in the number of patients who experienced heart failure hospitalization or cardiovascular mortality between the digoxin group and the placebo group (142 [29%] vs 154 [31%], respectively; HR, 0.88; 95% CI, 0.70 to 1.11; <i>P</i>=0.269).</p>
<p>Ahmed et al¹⁴</p> <p>Digoxin 0.125 to 0.5 mg Daily</p> <p>vs</p> <p>placebo Daily</p> <p>Patients continued on their other CHF therapies (including diuretics and ACE inhibitors)</p> <p>Initial dosing of digoxin was based on patient's age, sex, weight and renal function.</p>	<p>DB, MC, PC, RCT</p> <p>Patients with heart failure, regardless of ejection fraction, and who were in normal sinus rhythm.</p> <p>This was a post hoc analysis of a combination of the main DIG trial⁸ and the ancillary DIG trial⁹</p>	<p>N=5,548</p> <p>40 months</p>	<p>Primary: All-cause mortality</p> <p>Secondary: Mortality due to cardiovascular causes and heart failure, hospitalizations due to all causes, cardiovascular causes, and worsening heart failure</p>	<p>Primary: At 40 months, all cause death rate was 33% in the placebo group, 29% in the group of patients with a SDC 0.5 to 0.9 ng/mL, and 42% in the group of patients with a SDC ≥1.0 ng/mL (placebo vs SDC 0.5 to 0.9 ng/mL; adjusted HR, 0.77; 95% CI, 0.67 to 0.89; <i>P</i><0.0001 and placebo vs SDC ≥1.0 ng/mL; adjusted HR, 1.06; 95% CI, 0.93 to 1.20; <i>P</i>=0.406).</p> <p>Secondary: At 40 months, the cardiovascular mortality rate was 26% in the placebo group, 24% in the SDC 0.5 to 0.9 ng/mL group, and 33% in the SDC ≥1.0 ng/mL group (placebo vs SDC 0.5 to 0.9 ng/mL; adjusted HR, 0.83; 95% CI, 0.71 to 0.97; <i>P</i>=0.019 and placebo vs SDC ≥1.0 ng/mL; adjusted HR, 1.07; 95% CI, 0.93 to 1.24; <i>P</i>=0.339).</p> <p>At 40 months, the mortality rate due to heart failure was 12% in the placebo group, 9% in the SDC 0.5 to 0.9 ng/mL group, and 14% in the SDC ≥1.0 ng/mL group (placebo vs SDC 0.5 to 0.9 ng/mL; adjusted</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>HR, 0.63; 95% CI, 0.49 to 0.82; $P<0.0001$ and placebo vs SDC ≥ 1.0 ng/mL; adjusted HR, 0.87; 95% CI, 0.70 to 1.09; $P=0.236$).</p> <p>At 40 months, all cause hospitalization rates were 67% in the placebo group, 64% in the SDC 0.5 to 0.9 ng/mL group, and 71% in the SDC ≥ 1.0 ng/mL group (placebo vs SDC 0.5 to 0.9 ng/mL; adjusted HR, 0.85; 95% CI, 0.78 to 0.92; $P<0.0001$ and placebo vs SDC ≥ 1.0 ng/mL; adjusted HR, 0.95; 95% CI, 0.87 to 1.05; $P=0.331$).</p> <p>At 40 months, cardiovascular hospitalization rates were 53% in the placebo group, 48% in the SDC 0.5 to 0.9 ng/mL group, and 55% in the SDC ≥ 1.0 ng/mL group (placebo vs SDC 0.5 to 0.9 ng/mL; adjusted HR, 0.79; 95% CI, 0.72 to 0.88; $P<0.0001$ and placebo vs SDC ≥ 1.0 ng/mL; adjusted HR, 0.91; 95% CI, 0.82 to 1.01; $P=0.086$).</p> <p>At 40 months, hospitalization rates due to heart failure were 33% in the placebo group, 23% in the SDC 0.5 to 0.9 ng/mL group, and 29% in the SDC ≥ 1.0 ng/mL group (placebo vs SDC 0.5 to 0.9 ng/mL; adjusted HR, 0.62; 95% CI, 0.54 to 0.72; $P<0.0001$ and placebo vs SDC ≥ 1.0 ng/mL; adjusted HR, 0.68; 95% CI, 0.59 to 0.79; $P=0.086$).</p>
<p>Uretsky et al¹⁵</p> <p>Digoxin 0.125, 0.25, 0.375, or 0.5 mg Daily</p> <p>vs</p> <p>placebo Daily</p> <p>Digoxin was dosed to obtain a SDC of 0.9 to 2.0 ng/mL.</p> <p>Patients continued on background therapy of diuretics.</p>	<p>DB, MC, PC, PG, RCT</p> <p>Patients ≥ 18 years of age with NYHA Class II or III heart failure, normal sinus rhythm, receiving digoxin and diuretics, LVEF $\leq 35\%$, a LVED dimension of ≥ 60 mm or 34 mm/m²</p>	<p>N=88</p> <p>12 weeks</p>	<p>Primary: Treadmill time on maximal exercise testing, distance covered in a six-minute walking test, incidence of treatment failure, time to treatment failure</p> <p>Secondary: Change in signs and symptoms of heart failure, MLHF questionnaire,</p>	<p>Primary: At 12 weeks, patients in the placebo group experienced a median decline of 96.0 seconds in maximal exercise testing compared to a 4.5 second increase in the digoxin group ($P=0.003$).</p> <p>Digoxin did not display a significantly different effect on distance covered in a six-minute walking test (P value not reported).</p> <p>Patients in the placebo group experienced a 39% rate of treatment failures compared to 19% in the digoxin group ($P=0.039$). The patients in the placebo group also experienced a decreased time to treatment failure compared to the digoxin group ($P=0.037$). Treatment failures included hospital admissions, increase in drug therapy and death.</p> <p>Secondary: At the end of the 12-week study, there was not a statistically significant difference between the placebo and digoxin groups in changes in</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			heart failure score, seven-point GEP, LVEF, vital signs and body weight	<p>signs and symptoms of heart failure, MLHF questionnaire or heart failure score.</p> <p>At the end of 12 weeks, patients in the digoxin group experienced a mean increase in LVEF by 2%±2 compared to a mean decrease in LVEF of 3%±2 for the patients in the placebo group ($P=0.016$).</p> <p>Heart rate and body weight were significantly lower in the digoxin group compared to the placebo group ($P=0.03$ and $P=0.044$, respectively).</p>
<p>Packer et al¹⁶</p> <p>Digoxin Daily vs placebo Daily</p> <p>All patients started in an 8-week, single-blind run-in period during which the doses of background therapy for heart failure were adjusted to achieve optimal clinical benefits.</p> <p>After the run-in period, patients were randomized to either continue receiving digoxin therapy or receive placebo.</p> <p>Digoxin was dosed to obtain a SDC 0.9 to 2.0 ng/mL.</p> <p>Patients continued on background therapy of diuretics and an ACE inhibitor.</p>	<p>DB, MC, PC, RCT</p> <p>Patients ≥18 years of age with NYHA Class II or III heart failure, LVEF ≤35%, a LVED dimension of ≥60 mm or 34 mm/m², evidence of reduced exercise capacity, and normal sinus rhythm, who were clinically stable while receiving digoxin, diuretics, and an ACE inhibitor</p>	<p>N=178</p> <p>12 weeks</p>	<p>Primary: Rates of withdrawal from the study due to worsening heart failure, time to withdrawal, changes in exercise tolerance</p> <p>Secondary: Effects of discontinuing digoxin therapy on symptoms, quality of life, functional class, overall progress during the study and cardiac dimensions and function</p>	<p>Primary: Four patients who received digoxin, compared to 23 patients who received placebo, withdrew from the study due to worsening of heart failure ($P<0.001$). The patients in the placebo group had a higher risk of worsening heart failure compared to the patients in the digoxin group over the 12-week study (RR, 5.9; 95% CI, 2.1 to 17.2; $P<0.001$).</p> <p>Exercise tolerance remained stable in patients receiving digoxin compared to deterioration in exercise tolerance in patients receiving placebo. The median difference in exercise duration between the two groups after 12 weeks was 42 seconds ($P=0.006$).</p> <p>Exercise endurance remained constant in patients receiving digoxin compared to a decrease in patients receiving placebo. The median difference in submaximal exercise endurance between the two groups after 10 weeks was 41 meters ($P=0.01$).</p> <p>Secondary: Of the patients in the placebo group, 38% experienced worsening dyspnea and fatigue compared to 16% and 18% of patients in the digoxin group ($P=0.14$ and $P=0.04$, respectively). Thirty-three percent of patients in the placebo group experienced a less of an improved quality of life compared to 47% in the digoxin group ($P=0.04$). Also, 48% of patients in the placebo group experienced a more frequent decline in quality of life compared to 41% in the digoxin group ($P=0.04$).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				In the placebo group, 27% of patients were reported as having a deterioration in NYHA class compared to 10% of patients in the digoxin group ($P=0.019$). Thirty-one percent of patients in the placebo group reported that they felt moderately worse or much worse, compared to 9% of patients in the digoxin group ($P=0.007$).

Drug regimen abbreviations: BID=twice daily

Study abbreviations: DB=double-blind, MC=multicenter, OL=open label, PC=placebo-controlled, PG=parallel group, PRO=prospective, RCT=randomized controlled trial, XO=crossover

Miscellaneous abbreviations: ACE=angiotensin-converting enzyme, AF=Atrial Fibrillation, bpm=beats per minute, CHF=congestive heart failure, CI=confidence interval, DIG=Digitalis Investigation Group, ECG=electrocardiogram, ECV=electrical cardioversions, GEP=global evaluation of progress, HR=hazard ratio, INR=international normalized ratio, LVED=left ventricular end-diastolic, LVEF=left ventricular ejection fraction, MI=myocardial infarction, MLHF=Minnesota Living with Heart Failure, NYHA=New York Heart Association, OR=odds ratio, RR=relative risk, SDC=serum digoxin concentration

Special Populations**Table 5. Special Populations^{2,17}**

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Digoxin	Dose adjustment is required; an initial dose of 0.125 mg daily is recommended for >70 years of age with good renal function. Approved for use in premature infants up to children >10 years of age.	Renal dose adjustment is required; for impaired renal function, an initial dose of 0.125 mg daily is recommended; for severe renal impairment, an initial dose of 0.0625 mg daily is recommended; dose should be titrated every two weeks.	Not studied in hepatic dysfunction.	C	Yes

Adverse Drug Events

The adverse drug events reported with digoxin are dose dependant. Adverse events are less common when digoxin is used at recommended doses to achieve a therapeutic effect. It is also recommended that digoxin be used within the recommended therapeutic concentration range of 4.0 to 5.5 mmol/L and medications given concurrently be monitored closely to decrease the incidence of adverse drug events.²

Table 6. Adverse Drug Events²

Adverse Event	Digoxin
Cardiovascular	
Accelerated junctional rhythm	✓
Asystole	✓
Atrial tachycardia with block	✓
Atrioventricular dissociation	✓
Heart block (1st, 2nd, or 3rd degree)	✓
Palpitations	<1
PR prolongation	✓
ST segment depression	✓
Ventricular fibrillation	✓
Ventricular premature contractions, unifocal or multiform (especially bigeminy or trigeminy)	<1
Ventricular tachycardia	✓
Central Nervous System	
Anxiety	✓
Apathy	✓
Confusion	✓
Delirium	✓
Depression	✓
Dizziness	4.9
Fever	✓
Hallucinations	✓
Headache	3.2

Adverse Event	Digoxin
Mental disturbances	4.1
Visual disturbances (blurred or yellow vision)	✓
Dermatological	
Alopecia	✓
Edema (facial, angioneurotic, or laryngeal)	✓
Maculopapular rash	1.6
Pruritus	✓
Rash (bullous, erythematous, papular, scarlatiniform or vesicular)	✓
Shedding of fingernails or toenails	✓
Urticaria	✓
Endocrine and Metabolic	
Gynecomastia	<1
Plasma estrogen increased (men and postmenopausal women)	<1
Plasma testosterone decreased (men)	<1
Serum luteinizing hormone decreased (men and postmenopausal women)	<1
Sexual dysfunction	<1
Gastrointestinal	
Abdominal pain	✓
Anorexia	<1
Diarrhea	3.2
Nausea	3.2
Vomiting	1.6
Hematological	
Eosinophilia	<1
Thrombocytopenia	<1
Neuromuscular and Skeletal	
Weakness	✓
Other	
Hemorrhagic necrosis of the intestines	<1
Intestinal ischemia	<1
Vaginal cornification	<1

✓ Percent not specified.

Contraindications/Precautions

Digoxin is contraindicated in patients with a known hypersensitivity to digoxin or any component of digoxin. Also, digoxin is contraindicated in those with a hypersensitivity to cardiac glycosides (another may be tried); a history of toxicity; ventricular tachycardia or fibrillation; idiopathic hypertrophic subaortic stenosis; constrictive pericarditis; amyloid disease; second- or third-degree heart block (except in patients with a functioning artificial pacemaker); Wolff-Parkinson-White syndrome and atrial fibrillation concurrently. Toxicity may occur in patients with hypokalemia or hypomagnesemia despite concentrations below 0.2 ng/mL. Hypothyroidism may decrease the requirements for digoxin. Digoxin should be used with caution in patients with acute myocardial infarction and avoided in patients with myocarditis.²

Drug Interactions

Any drug that may decrease renal function may decrease the excretion of digoxin; therefore, caution should be exercised in patients who are taking these agents concurrently with digoxin. The manufacturer lists several potential drug interactions that may be seen with concurrent therapy with digoxin. Agents such as alprazolam, amiodarone, indomethacin, itraconazole, propafenone, quinidine, rifampin, spironolactone, and verapamil may reduce the clearance, and therefore, may cause an increase in serum digoxin levels. Clarithromycin, erythromycin, and tetracycline may increase digoxin absorption in patients who inactivate digoxin by bacterial metabolism in the lower intestine, resulting in an increase in serum digoxin levels. Also, antacids, certain anticancer drugs, kaolinpectin, neomycin and sulfasalazine may interfere with the intestinal absorption of digoxin, which may lead to lower serum digoxin levels.²

Table 7. Drug Interactions²

Drug(s)	Interaction	Mechanism
Digoxin	Amiodarone	Mechanism of interaction is unknown but it is thought that multiple mechanisms are involved. Serum digoxin levels may be increased, resulting in an increase in the pharmacologic and toxic effects of digoxin.
Digoxin	Cholestyramine	Cholestyramine may decrease the gastrointestinal absorption of digoxin by binding to it. Cholestyramine may also interrupt the enterohepatic recycling of digoxin.
Digoxin	Metoclopramide	Metoclopramide may decrease the absorption of digoxin by increasing gastrointestinal motility.
Digoxin	Propafenone	Actual mechanism of the interaction is unknown. The volume of distribution of digoxin may be decreased along with a decrease in the renal and non-renal clearance which may increase serum digoxin levels, resulting in toxicity.
Digoxin	Quinidine	Quinidine may reduce the renal clearance, biliary clearance and volume of distribution of digoxin thereby increasing serum digoxin levels and increasing the risk of toxicity.

Dosage and Administration

Several factors must be taken into account when dosing digoxin including the patient's lean body weight, renal function, age, concomitant disease states, concurrent medications, or other factors that may alter the pharmacokinetic properties of digoxin.

Table 8. Dosing and Administration²

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Digoxin	<p><u>Treatment of mild to moderate heart failure (rapid digitalization):</u> Tablet: 0.5 to 0.75 mg orally; monitor response; additional doses of 0.125 to 0.375 mg orally may be given cautiously at six to eight hour intervals to achieve response; maintenance or gradual digitalization, give 0.125 to 0.5 mg once daily, titrate every two weeks</p> <p>Intravenous injection: 0.4 to 0.6 mg; additional doses of 0.1 to 0.3 mg may be given cautiously at six to eight hour intervals to achieve response; maintenance or gradual digitalization, give 0.1 to 0.4 mg once daily, titrate every two weeks</p> <p>Elixir: Maintenance, 3 µg/kg daily, adjust as necessary</p> <p><u>Treatment of mild to moderate heart failure (without loading dose):</u> Tablet or elixir: initial, 0.25 mg orally once daily; maintenance, 0.125 to 0.5 mg orally once daily; titrate dose every two weeks</p>	<p><u>Treatment of mild to moderate heart failure (rapid digitalization):</u> Intravenous injection (give in divided doses): premature, 15 to 25 µg/kg; full-term, 20 to 30 µg/kg; 1 to 24 months, 30 to 50 µg/kg; 2 to 5 years, 25 to 35 µg/kg; 5 to 10 years, 15 to 30 µg/kg; over 10 years, 8 to 12 µg/kg</p> <p>Elixir (give in divided doses): premature, 20 to 30 µg/kg; full-term, 25 to 35 µg/kg; 1 to 24 months, 35 to 60 µg/kg; 2 to 5 years, 30 to 40 µg/kg; 5 to 10 years, 20 to 35 µg/kg; over 10 years, 10 to 15 µg/kg</p> <p><u>Treatment of mild to moderate heart failure (maintenance dose or gradual digitalization):</u> Intravenous injection, elixir (give in divided doses): premature, 20 to 30% of intravenous digitalizing dose; all other pediatrics, 25 to 35% of oral or intravenous digitalizing dose</p>	<p>Elixir: 50 µg/mL</p> <p>Injection: 100 µg/mL 250 µg/mL</p> <p>Tablet: 125 µg 250 µg</p>

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	<u>Control of ventricular response rate in patients with chronic atrial fibrillation:</u> Elixir, intravenous injection, tablet: loading dose, 0.25 mg every two hours; maximum, 1.5 mg; maintenance dose, 0.125 to 0.375 mg orally daily or 0.125 to 0.25 mg intravenously daily	Tablet (give in divided doses): 2 to 5 years, 10 to 15 µg/kg; 5 to 10 years, 7 to 10 µg/kg; over 10 years, 3 to 5 µg/kg <u>Control of ventricular response rate in patients with chronic atrial fibrillation:</u> Usual dose, 8 to 12 µg/kg; dose should be titrated to the minimum dose that achieves the desired ventricular rate control without causing undesirable side effects	

Clinical Guidelines

The role of digoxin in therapy has changed over the last decade. McNamara and colleagues published a background review summarizing the evidence of the efficacy of medications to treat atrial fibrillation which supports the recommendations provided by current guidelines.¹⁸ Also, many guidelines that have been published by particular organizations are endorsed by other organizations, for example, the American College of Chest Physicians endorses the American College of Cardiology/American Heart Association guideline update for the diagnosis and management of chronic heart failure.¹⁹ Current guidelines are summarized in Table 9. Due to the complexity of treatment regimens for atrial fibrillation and heart failure, the associated guideline summaries focus on the role of digoxin in disease management.

Table 9. Clinical Guidelines

Clinical Guideline	Recommendation(s)
American College of Cardiology/American Heart Association/ European Society of Cardiology Committee for Practice Guidelines: Focused Updated on the Management of Patients with Atrial Fibrillation (Updating 2006 Guideline²⁰) (2011)²¹	<ul style="list-style-type: none"> • Oral digoxin may effectively control the heart rate at rest in patients with atrial fibrillation and is indicated for patients with heart failure, left ventricular dysfunction, or for sedentary individuals. • Digoxin is no longer considered first-line therapy for rapid management of atrial fibrillation, except in patients with heart failure or left ventricular dysfunction, or perhaps in patients who are so sedentary as to obviate the need for rate control during activity because there are more effective agents that are now available. • To control heart rate, digoxin use concurrently with either a β-blocker or nondihydropyridine calcium channel blocker is reasonable in patients with atrial fibrillation, both at rest and during exercise. The medication chosen should be individualized and bradycardia should be avoided by closely monitoring and changing digoxin therapy. • Concurrent use of digoxin and β-blockers appears to be more effective than the concurrent use of digoxin and a calcium channel blocker. • It is not recommended to use digoxin for pharmacological cardioversion of atrial fibrillation as harm may be caused. • Digitalis glycosides have not been proven to be more efficacious than placebo for the conversion of recent-onset atrial fibrillation to sinus rhythm. Digoxin may actually prolong the duration of paroxysmal atrial fibrillation episodes in some patients. • Evidence does not support the use of digitalis to suppress recurrent atrial fibrillation in most patients. • Digoxin, a β-blocker, or a nondihydropyridine calcium channel blocker are all options and are recommended in pregnancy to control ventricular

Clinical Guideline	Recommendation(s)
<p>National Institute for Health and Clinical Excellence: Atrial Fibrillation (2006)²²</p>	<p>response rate.</p> <ul style="list-style-type: none"> • For patients who need rate control for chronic atrial fibrillation, β-blockers and calcium channel blockers are first line agents. Digoxin should only be used as first line in sedentary patients or in those who cannot tolerate β-blockers or calcium channel blockers. • For patients who are prescribed digoxin alone for rate control, a diagnosis should be written on the prescription. • Combination therapies such as digoxin and β-blocker or digoxin and calcium channel blocker may be considered once a patient has failed monotherapy. • Digoxin has been proven to be ineffective in pharmacological cardioversion and therefore is determined to be an inappropriate therapy for this indication. • Digoxin should not be used in atrial fibrillation patients who are hemodynamically unstable due to its slow onset of action. • The use of digoxin in patients with Wolff-Parkinson-White syndrome is contraindicated due to the potential of exacerbating a rapid atrial fibrillation. • Digoxin has not been clinically proven to be effective in preventing postoperative atrial fibrillation therefore should not be used in this indication.
<p>American College of Cardiology/American Heart Association: Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult (2005)¹⁹ and Diagnosis and Management of Heart Failure in Adults (2009 Focused Update)²³</p>	<ul style="list-style-type: none"> • The safety and efficacy of digoxin does not compare favorably with that of other agents such as aldosterone blockers. • Digoxin may be added to concurrent therapy with diuretics, an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), and a β-blocker in those patients with persistent heart failure symptoms or in those patients who have not yet responded to this initial therapy. • Digoxin therapy may be delayed until the patient remains symptomatic despite therapy with the neurohormonal antagonists or delay digoxin therapy until the symptomatic patient has tried and did not respond or could not tolerate aldosterone antagonist as well. • Digoxin should be considered an adjunct therapy to β-blockers for rate control because β-blockers improve survival and may be effective at controlling rate alone. • In patients with an acute exacerbation of heart failure symptoms, the patient should be initially treated with appropriate HF therapy, and once stable, digoxin may be initiated as part of a long-term treatment plan. • Digoxin should be avoided in patients with significant sinus or atrioventricular block (unless patient has pacemaker) and it should be used cautiously in patients who are on other agents that may suppress sinus or atrioventricular nodal function or affect digoxin levels.
<p>Heart Failure Society of America: Heart Failure Society of America 2010 Comprehensive Heart Failure Practice Guidelines (Executive Summary) (2010)²⁴</p>	<ul style="list-style-type: none"> • Digoxin should be considered for patients with left ventricular systolic dysfunction (left ventricular ejection fraction [LVEF] $\leq 40\%$) who have signs or symptoms of heart failure while receiving standard therapy, including ACE inhibitors and β-blockers. • It is recommended that the dose of digoxin, which should be based on lean body mass, renal function and concomitant medications, should be 0.125 mg daily in the majority of patients and the serum digoxin level should be <1.0 ng/mL, generally 0.7 to 0.9 ng/mL. • Doses >0.25 mg daily, for the purpose of rate control, are not recommended. • Digoxin should be considered for adequate control of the ventricular

Clinical Guideline	Recommendation(s)
	<p>response to atrial fibrillation in patients with heart failure.</p> <ul style="list-style-type: none"> For patients taking amiodarone and digoxin concurrently, it is recommended that the maintenance dose of digoxin be reduced when amiodarone is initiated and then carefully monitored for the possibility of adverse drug interactions. Adjustment in doses of these drugs and laboratory assessment of drug activity or serum concentration after initiation of amiodarone is recommended.
<p>European Society of Cardiology: European Society of Cardiology Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure (2008)²⁵</p>	<ul style="list-style-type: none"> Digoxin may be used in patients with symptomatic heart failure and atrial fibrillation to slow a rapid ventricular rate. It should be used in addition to, or prior to a β-blocker in patients with atrial fibrillation and LVEF $\leq 40\%$. Digoxin in addition to an ACE inhibitor may reduce hospitalizations for worsening heart failure and improve ventricular function and patient wellbeing, in the patients in sinus rhythm with symptomatic heart failure and LVEF $\leq 40\%$, but has no effect on mortality. Digoxin is useful for initial control of the ventricular rate in patients with rapid atrial fibrillation and may be considered decompensated heart failure patients prior to initiation of a β-blocker. In patients with LVEF $>40\%$, verapamil or diltiazem may be used either alone or in combination with digoxin to control ventricular rate. Digoxin or a β-blocker is recommended to control heart rate at rest in patients with heart failure and left ventricular dysfunction. A combination of digoxin and a β-blocker may be considered to control heart rate at rest and during exercise. In hemodynamically unstable patients, digoxin is recommended as initial treatment in left ventricular systolic dysfunction. In patients with atrial fibrillation and heart failure who do not have an accessory pathway, intravenous administration of digoxin or amiodarone is recommended to control heart rate. A non-dihydropyridine, alone or in combination with digoxin, should be considered to control heart rate at rest and during exercise in patients with heart failure and preserved LVEF. Digoxin doses may need adjustment in elderly patients so that there is a lower risk of adverse effects. This same principle should be applied to patients with elevated serum creatinine.

Conclusions

Digoxin is a Class IV antiarrhythmic agent derived from a species of Digitalis or foxglove, plants whose medical use was described over two centuries ago.¹ It is Food and Drug Administration approved for the treatment of atrial fibrillation and heart failure. For the treatment of atrial fibrillation, digoxin applies its effects by increasing contractility via inhibition of the Na⁺ and K⁺ ATPase pump. The effects of digoxin in heart failure are mediated by its direct suppression of the atrioventricular node. Although there are minor differences with respect to pharmacokinetic parameters, all digoxin products are equally effective. Due to its potential for drug interactions and other toxicities, digoxin therapy should be monitored closely.

Currently, there are several guidelines that discuss the role of digoxin therapy for the treatment of atrial fibrillation and heart failure. According to the current treatment guidelines for atrial fibrillation, β -blockers and calcium channel blockers are considered first-line agents and digoxin is recommended as a second- or third-line agent. Digoxin may be used in specific patient populations including those that are sedentary, those who have concurrent heart failure, or those who cannot tolerate or have failed single therapy with β -blockers and calcium channel blockers. In the current guidelines for the treatment of heart failure, it is recommended that digoxin may be added to standard therapy in those patients who continue to have

symptoms of heart failure. In those patients with concurrent symptomatic heart failure and atrial fibrillation, digoxin should be used as the first-line agent.¹⁸⁻²⁵

Appendix I: Utilization Within This Drug Class for DVHA: January 1, 2011 to June 30, 2011

Medication	Unique utilizers	# of Rx's	Market Share (%)	Plan Cost \$	Avg \$/Rx
Digoxin	80	176	95.65%	\$2,793.97	\$15.87
Lanoxin	3	8	4.35%	\$102.05	\$12.76
Class Total:	83	184	100%	\$2,896.02	\$15.74

Recommendations

Currently all cardiotoxic agents are listed as preferred on the Department of Vermont Health Access (DVHA) preferred drug list (PDL). No changes to the DVHA approval criteria for cardiotoxic agents are proposed.

References

1. Parker RB, Patterson JH, Johnson JA. Heart Failure. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, editors. *Pharmacotherapy: a pathophysiologic approach*. 6th ed. New York (NY): McGraw-Hill; 2005. p. 219-60.
2. Lanoxin® [package insert]. Research Triangle Park (NC): GlaxoSmithKline; 2009 Aug.
3. Digoxin: drug information. In: Basow DS (Ed). UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2011 [cited 2011 May 2]. Available from: <http://www.uptodate.com/utd/index.do>.
4. Hallberg P, Lindbäck J, Lindahl B, Stenesstrand U, Melhus H; RIKS-HIA group. Digoxin and mortality in atrial fibrillation: a prospective cohort study. *Eur J Clin Pharmacol*. 2007 Oct;63(10):959–71.
5. Khand AU, Rankin AC, Martin W, Taylor J, Gemmell I, Cleland JG. Carvedilol alone or in combination with digoxin for the management of atrial fibrillation in patients with heart failure? *J Am Coll Cardiol*. 2003 Dec 3;42(11):1944–51.
6. Koh KK, Song JH, Kwon KS, Park HB, Baik SH, In HH, et al. Comparative study of efficacy and safety of low-dose diltiazem or betaxolol in combination with digoxin to control ventricular rate in chronic atrial fibrillation: randomized crossover study. *Int J Cardiol*. 1995 Nov 24;52(2):167–74.
7. Hemels ME, Van Noord T, Crijns HJ, Van Velduisen DJ, Veeger NJ, Bosker HA, et al. Verapamil versus digoxin and acute versus routine serial cardioversion for the improvement of rhythm control for persistent atrial fibrillation. *J Am Coll Cardiol*. 2006 Sep 5;48(5):1001–9.
8. The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med*. 1997 Feb 20;336(8):525-33.
9. Ahmed A, Rich MW, Fleg JL, Zile MR, Young JB, Kitzman DW, et al. Effects of digoxin on morbidity and mortality in diastolic heart failure: The ancillary Digitalis Investigation Group trial. *Circulation*. 2006 Aug 1;114(5):397-403.
10. Wyse DG, Waldo AL, DiMarco JP, et al. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med*. 2002;347(23):1825-33.
11. Van Gelder IC, Hagens VE, Bosker HA, et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med*. 2002;347(23):1834
12. Opolski G, Torbicki A, Kosior DA, et al. Rate control vs rhythm control in patients with nonvalvular persistent atrial fibrillation: The results of the polish how to treat chronic atrial fibrillation (HOT CAFE) Study. *Chest*. 2004;126:476–86.
13. Koh KK, Kwon KS, Park HB, Baik HB, Park SJ, Lee KH, et al. Efficacy and safety of digoxin alone and in combination with low-dose diltiazem or betaxolol to control ventricular rate in chronic atrial fibrillation. *Am J Cardiol*. 1995 Jan1;75(1):88-90.
14. Ahmed A, Rich MW, Love TE, Lloyd-Jones DM, Aban IB, Colucci WS, et al. Digoxin and reduction in mortality and hospitalization in heart failure; a comprehensive post hoc analysis of the DIG trial. *Eur Heart J*. 2006 Jan;27(2):178-86.
15. Uretsky B, Young JB, Shahidi FE, Yellen LG, Harrison MC, Jolly MK, et al. Randomized study assessing the effect of digoxin withdrawal in patients with mild to moderate chronic heart failure: Results of the PROVED trial. *J Am Coll Cardiol*. 1993 Oct;22(4):955-62.
16. Packer M, Gheorghiade M, Young JB, Constantini PJ, Adams KF, Cody RJ, et al. Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-converting enzyme inhibitors. *N Engl J Med*. 1993 Jul 1;329(1):1-7.
17. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Reuters (Healthcare) Inc.; Updated periodically [cited 2011 May 2]. Available from: <http://www.thomsonhc.com/>.
18. McNamara RL, Tamariz LJ, Segal JB, Bass EB. Management of atrial fibrillation: Review of the evidence for the role of pharmacologic therapy, electrical cardioversion, and echocardiography. *Ann Intern Med*. 2003 Dec 16;139(12):1018-33.
19. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, et al. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): Developed in collaboration with the American College of Chest Physicians and the

- International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. *Circulation*. 2005 Sep 20;112 (12);e154-e235.
20. Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation*. 2006 Aug 15;114(7):e257-e354.
 21. Wann LS, Curtis AB, January CT, Ellenbogen KA, Lowe JE, Estes NAM, et al. 2011 ACCF/AHA/HRS focused updated on the management of patients with atrial fibrillation (updating 2006 guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2011 Jan 11;57(2):223-42.
 22. National Institute for Health and Clinical Excellence (NICE). Atrial Fibrillation [guideline on the Internet]. London (UK): National Institute for Health and Clinical Excellence, 2006 Jun [cited 2008 Jan 30]. Available from: <http://www.nice.org.uk/nicemedia/pdf/cg036fullguideline.pdf>.
 23. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, et al. 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. *Circulation*. 2009 Apr 14;119(14):e391-479.
 24. Heart Failure Society of America, Lindenfeld J, Albert NM, Boehmer JP, Collins SP, Ezekowitz JA, Givertz MM, et al. HFSA 2010 Comprehensive Heart Failure Practice Guideline. *J Card Fail*. 2010 Jun;16(6):e1-194.
 25. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur J Heart Fail*. 2008 Oct;10(10):933-89.