

## Digoxin: the good and the bad

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## **Abstract**

After 230 years of use, digitalis remains an important and useful therapy for patients with atrial fibrillation, heart failure and the 30-50 % of patients with both conditions. Although the combination of positive inotropic activity with negative chronotropic effects have been shown to reduce hospital admissions in heart failure, there is a distinct lack of robust trial data, particularly in patients with atrial fibrillation. We recently performed a comprehensive meta-analysis of all digoxin studies and demonstrated a neutral effect on mortality. This contradicts prior observational data that overlooks the fact that digitalis is usually given as second-line therapy to the sickest patients. Use of these agents in clinical practice should take account of appropriate dose, serum concentration, drug interactions and potential side effects. The aim of this review is to evaluate the evidence base for cardiac glycosides and provide a pragmatic guide to their advantages and disadvantages.

## **Abbreviations**

ACEI	Angiotensin Converting Enzyme Inhibitor
AF	Atrial Fibrillation
AHA	American Heart Association
ARB	Angiotensin 2 Receptor Blocker
AVN	Atrioventricular Node
CI	Confidence Interval
CKD	Chronic Kidney Disease
CO	Cardiac Output
CRT	Cardiac Resynchronisation Therapy
HFpEF	Heart Failure with preserved Ejection Fraction
HFrEF	Heart Failure with reduced Ejection Fraction
HR	Hazard Ratio
LVEF	Left Ventricular Ejection Fraction
NYHA	New York Heart Association
OR	Odds Ratio
PCWP	Pulmonary Capillary Wedge Pressure
RCT	Randomised Controlled Trial
RR	Relative Risk
SDC	Serum Digoxin Concentration

## Introduction

Sir William Withering first described the use of the foxglove plant, *Digitalis purpurea*, for heart failure (HF) in Birmingham, UK in 1785 (1). Over two centuries later, cardiac glycosides are still widely used as a positive inotrope in HF and for its negative chronotropic activity in atrial fibrillation (AF). A small number of randomised controlled trials (RCTs) have provided evidence to support the use of digoxin in patients with HF due to reduced ejection fraction (HFrEF) (2). Notably the Digoxin Investigators' Group (DIG) trial showed that digoxin improved symptoms and reduced hospitalisation rates without any impact on all-cause mortality (3,4). Following the availability of therapies providing prognostic benefit in HFrEF (including angiotensin converting enzyme inhibitors, beta-blockers, aldosterone antagonists and cardiac resynchronisation therapy), prescription rates of digoxin have fallen substantially (5,6). However, there were high rates of concomitant digoxin use in the trials of these agents. For example, in the major beta-blocker RCTs, an average of 58% of participants were on digoxin at baseline (range 9% to 92%) (7).

The publication of numerous observational studies reporting increased mortality with digoxin have intensified clinical concern. In the OPTIMIZE-HF registry only 30% of patients with HFrEF were prescribed digoxin prior to hospitalisation. By discharge, digoxin was only prescribed in a further 8%, despite the presence of on-going symptoms on guideline-recommended therapy (8). However, observational trials of digoxin are flawed by unavoidable prescription bias, with clear disparity in baseline characteristics between those patients given digoxin and the control groups (typically no therapy) (2). Furthermore, post-hoc analyses of the DIG trial have demonstrated a decrease in mortality amongst those with low serum digoxin levels (3,9).

In this article, we address the evidence for digoxin in HF and AF populations, and highlight the advantages and limitations which guide clinical decisions about the use of this therapy.

## **Mechanism of action**

Digitalis has three key pharmacological mechanisms of action; haemodynamic, neurohormonal and electrophysiological (**Figure 1**). Firstly, digitalis reversibly inhibits the membrane bound alpha subunits of the sodium-potassium ATPase pump in cardiomyocytes (10). The resulting increased intracellular sodium concentration promotes activity of the sodium calcium exchanger, increasing intracellular calcium concentration. Greater interaction between the myocardial contractile proteins improves the force of contraction leading to a global increase in left ventricular systolic function (11). When intravenous digoxin is administered acutely in patients with HFrEF in sinus rhythm, there is a short-term improvement in cardiac output, left ventricular ejection fraction (LVEF), stroke index, pulmonary capillary wedge pressure, exercise tolerance and peak VO<sub>2</sub> (12,13). Secondly, digitalis induces vagal activation leading to a shift in autonomic balance towards parasympathetic dominance. The pathophysiology of HF includes an initial compensatory and later detrimental neurohormonal activation. Digoxin modulates these neurohormonal abnormalities, reducing plasma norepinephrine. The mechanism for this direct anti-sympathetic activity has not been fully elucidated, but is likely to reflect attenuation and sensitisation of the pathologically augmented baroreflex in HF patients with raised filling pressures (14,15).

Finally, inhibition of the sodium-potassium ATPase by digoxin slows the heart rate. Whether heart rate is a determinant of prognosis in HF patients or simply an indicator for increased sympathetic tone is contentious. However, ivabradine, a drug that acts solely to reduce heart rate (without evidence for substantial modulation of neurohormonal response), has been shown to improve prognosis in HF patients with sinus rhythm (16). Digitalis exerts a parasympathomimetic action on the sinoatrial node and atrioventricular node (AVN), slowing their conduction and increasing the refractory period. Importantly during exercise, or whenever there is increased sympathetic activity, the rate controlling effects of digitalis are overcome. The sodium-potassium ATPase is targeted by a variety of endogenous and exogenous cardiac glycosides and cardiotonic steroids, with increasing titres of the latter seen in disease states (17). Differing levels of endogenous cardiotonic steroids

may partly explain the varied susceptibility to digoxin toxicity, including competition for molecular targets and conformational changes that lead to synergism or antagonism (18,19).

The collective properties of digitalis make it unique in being able to positively influence cardiac inotropy, whilst simultaneously constraining the chronotropic action of the heart. However, the digoxin plasma level determines which of these mechanisms predominates; although haemodynamic effects are very limited at low levels, significant reductions in norepinephrine are still observed (15).

Around 80% of oral digoxin is absorbed, principally in the proximal small intestine, and then 20-30% is bound to serum albumin. Digoxin undergoes widespread dissemination into the tissues, particularly the myocardium, kidneys and skeletal muscle. The half-life in healthy individuals is 26-45 hours, with renal excretion being the principle route of elimination (20).

## **Evaluating the evidence base**

Digoxin is particularly prone to prescription bias, as clinicians tend to use digoxin in sicker patients. Since digoxin is not recommended as first-line therapy for either AF or HF, it is usually only prescribed when physicians recognise clinical deterioration in patients already receiving therapy. Thus, the prescribing of digoxin is prone to being influenced by the likelihood of death, creating a scenario of “confounding by indication.” This results in profound differences in baseline characteristics between digoxin and control groups in observational studies, distorting the analysis of clinical outcomes (**Figure 2**) (2). Although statistical adjustment for known confounders is possible, important residual confounders can be unknown or masked. When treatment and control groups differ vastly in characteristics, reliable effect estimates are not possible, even for

sophisticated techniques such as propensity-score matching (21). This reinforces the need for well-designed RCTs to guide decisions on clinical therapy.

## **Evidence underpinning the use of digitalis**

### **Heart failure**

Heart failure is a common and costly condition with increasing prevalence and high mortality (22). In HFrEF, there are clinical trials that have examined the efficacy of digoxin compared to placebo, vasodilators, and other inotropes.

The DIG trial is currently the largest and most rigorous assessment of digoxin in HFrEF patients with sinus rhythm, including 6,800 participants with LVEF  $\leq 45\%$  randomised to digoxin or placebo. All patients were treated with ACE inhibitors and diuretics and the mean digoxin dose was 250 micrograms (3). After 37 months follow-up, there was no difference in all-cause mortality between digoxin and placebo groups (34.8% vs 35.1%; risk ratio 0.99, 95% CI 0.91-1.07), but digoxin led to a small but significant reduction in all-cause hospitalisation (64.3% vs 67.1%, risk ratio 0.92, 95% CI 0.87-0.98). These findings have been replicated in other RCTs, as demonstrated by a comprehensive meta-analysis (**Figure 3**), which also exposes how observational data can be misleading due to marked differences in patients receiving digoxin and control therapy (2).

Three placebo-controlled trials compared the effect of digoxin withdrawal with continuation in patients with stable HFrEF (23-25). All showed that withdrawal from digoxin leads to a deterioration in exercise tolerance, worsening HF and a reduction in ejection fraction (24-26).

Pooled analysis demonstrated that triple therapy with digoxin, ACE inhibitors and diuretic reduced the risk of worsening HF, with digoxin contributing to a significant cost reduction (27,28). A meta-analysis of studies stopping HF medications confirmed that digoxin withdrawal increased HF hospitalisation (RR 1.30, 95% CI 1.16-1.46) but had no impact on all-cause mortality (RR 1.00, 95% CI 0.90-1.12) (29).



European and American guidelines indicate that digoxin is beneficial in patients with HFrEF to reduce HF hospitalisations (**Table 1**) (22,30). Digoxin is recommended for persistent symptoms despite optimal therapy or as an alternative or adjunct to reduce hospitalisation. Since digoxin provides symptomatic relief but no survival benefit, it is not indicated in asymptomatic patients. Digoxin is rarely useful for *acute* stabilisation of symptomatic patients with decompensated HF, who should be managed with diuretics, nitrate therapy and possibly inotropes. In patients already taking digoxin, it is advisable to avoid withdrawal, and digoxin should be continued throughout introduction of ACE inhibitors and other first-line HF agents.

Patients with heart failure with preserved ejection (HFpEF) have received less attention. Around half of patients with heart failure have HFpEF, but as yet, there are no therapies known to reduce mortality. This also applies to digoxin, as shown by the ancillary DIG trial, which included 988 patients with HFpEF (LVEF >45%) and sinus rhythm. Digoxin was associated with a non-significant trend towards reduction in HF hospitalisation (hazard ratio [HR] 0.79, 95% CI 0.59-1.04), but this was counterbalanced by a trend towards increased hospitalisations for unstable angina (HR 1.37, 95% CI 0.99-1.91) (4). Further studies on concomitant HFpEF and AF are urgently needed to better inform clinical practice.

### **Atrial fibrillation**

Atrial fibrillation is the most common arrhythmia, with rapidly increasing prevalence (31).

Management involves prevention of stroke and systemic embolization, restoring sinus rhythm in selected patients and control of heart rate. Rate control is achieved using drugs that slow conduction across the AVN, such as beta-blockers, non-dihydropyridine calcium channel blockers (diltiazem or verapamil), and digoxin. Unfortunately, there are limited comparative data available

to choose appropriate therapy for individual patients (32,33). At present there are no randomised, head-to-head studies of digoxin in patients with AF.

As previously mentioned, observational data are confounded and not suitable to make clinical decisions on treatments such as digoxin, which is typically given to the sickest individuals (2). This has not stopped researchers from attempting to meta-analyse observational data, which unsurprisingly show that digoxin is associated with increased mortality in AF patients (**Table 2**) (2,29,34-40). These findings are incongruous with data in patients with HFrEF plus AF (see below) and the reduction in hospital admissions in HF. Remarkably, three different post-hoc analyses of the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) dataset demonstrated divergent findings for digoxin, highlighting the problems of using observational data (41-43). Until further RCTs are available, digoxin remains an important contribution to achieving rate control in AF patients. Clinical guidelines for AF suggest digoxin as second-line therapy, after beta-blockers, verapamil and diltiazem (**Table 1**) (44-46).

### **Concomitant heart failure and atrial fibrillation**

Heart failure and AF share pathophysiology, increasing the risk of the other condition, and hence frequently co-exist in clinical practice (47). Irrespective of which comes first, this combination considerably worsens prognosis (48). Although concomitant HFrEF with AF is associated with higher all-cause mortality than HFpEF with AF, patients have similar rates of stroke and hospital admission (49).

In general, patients with HF and AF have been underrepresented in clinical trials and management of these patients has typically followed that of HF, overlooking the impact that AF has on the efficacy of available therapies and interventions. For example, beta-blockers were shown to have no significant effect on mortality or hospitalisation in HFrEF patients with concomitant AF in an

individual patient data meta-analysis of all major placebo-controlled RCTs (7). The adjusted HR for death was 0.97 (95% CI 0.83-1.14), markedly different to the benefit seen in patients with sinus rhythm (HR 0.73, 95% CI 0.67-0.80), and with a highly significant p-value for interaction of baseline heart rhythm (p=0.002). This has led to questions about what alternatives clinicians have available for rate control, particularly as verapamil and diltiazem have negatively inotropic effects on the failing myocardium and can potentially increase adverse outcomes (50).

Unfortunately, trial evidence to clearly define the place of digoxin in the clinical management of these patients is limited. Only a handful of studies have assessed the impact of digoxin on mortality in patients with HF and AF, all of which are observational (51-54). The HR for all-cause mortality with digoxin compared to control in meta-analysis of two studies with standard baseline adjustment was 0.90 (95% CI 0.70-1.16) and 1.08 (95% CI 0.93-1.26) in two studies with propensity matching (2). Therefore, although based on suboptimal data, there is no suggestion that digoxin increases mortality in patients with concomitant HF and AF, and in fact we observed similar effects to that seen in HF patients without AF. In a large prospective registry of AF patients in the United States, there was no increase in mortality or hospitalisation in patients using digoxin, with or without HF (55). A single RCT of 47 patients has examined digoxin and beta-blockers in patients with HFrEF and persistent AF (56). Double-blinded withdrawal of digoxin led to a decline in LVEF and increase in BNP, although the size of the trial limits further conclusions. Relevant guidelines are presented in **Table 1** and data from other observational meta-analyses are summarised in **Table 2**.

### **Practical use of digoxin**

Cardiac glycosides are one of the more challenging cardiovascular therapies to prescribe and administer. In this section, we describe some of the practical considerations involved, including dose, serum digoxin concentration (SDC), drug interactions and adverse treatment effects.

### ***1. Dose and serum concentrations***

The dose of cardiac glycoside required (digoxin or digitoxin) depends on the clinical indication. For example, acute heart rate control requires rapid loading with higher doses via the intravenous route, whereas control of HF symptoms can be achieved with smaller doses and a longer time to steady-state through the oral route (**Table 3**).

Although digoxin dose correlates well with serum concentration, in patients with low muscle mass or renal impairment the serum concentration relative to the dose will be proportionally increased. A quantitative SDC can be measured in most hospitals using a standard radioimmunoassay. However, SDC monitoring is highly impractical, with samples required 8-12 hours post-dose to ensure adequate distribution. Blood collected prior to this will show a falsely elevated SDC. Since it takes time for digoxin to achieve steady state, SDC should not be measured for at least 7 days following initiation or alteration in dose. There is a linear relationship between digoxin dose and SDC, but accurately adjusting the dose relies on blood being collected at the correct time, under stable renal function. Even when SDC is in the optimal therapeutic range (0.5-0.9 ng/mL), patients have demonstrated clinical signs of toxicity, and conversely asymptomatic patients with “toxic” SDCs have been reported (57). Thus, given the poor correlation between SDC and clinical findings, digoxin intoxication remains a clinical diagnosis. Other concerns include digoxin-like immunoreactive substances causing falsely elevated levels in pregnancy, newborns, acromegaly, liver disease and renal failure (58).

The association between dose, SDC and clinical outcomes with digoxin is poorly described and only post-hoc analyses of limited patient numbers are available. In the DIG trial, results were suggestive of reduced mortality with SDC at one-month of <0.9 ng/mL, and higher mortality with SDC  $\geq$ 1.2 ng/ml (9,59). In pooled analysis of two smaller RCTs however, there was no association between SDC and clinical outcomes (60). It should be highlighted that these post-hoc analyses of

SDC are confounded by the fact that sicker patients may require a higher digoxin dose and higher SDC could reflect poorer baseline cardiac or renal function. However, when appraised together, most clinicians would agree that low-dose digoxin therapy, avoiding high or toxic SDC, is the most appropriate use of this therapy.

## **2. Patients with chronic kidney disease**

Renal disease results in prolongation of the half-life of digoxin as 70 to 80% of the drug is eliminated unchanged in the urine (with the remainder undergoing hepato-biliary clearance) (61). Renal insufficiency also reduces the extravascular volume of distribution of digoxin, elevating SDC as mentioned above. Thus, in patients with underlying renal disease the dose should be modified and regular SDC monitoring should be implemented. Both the initial loading dose and maintenance dose must be reduced with the loading dose reduced by 33-50% in severe renal insufficiency, including haemodialysis (62). The initial maintenance dose should be determined by the ideal body weight and creatinine clearance and plotted against a normogram (63). Chronic kidney disease is more common in patients most in need of digoxin, are therefore those most vulnerable to toxicity.

## **3. Drug interactions**

Interactions with digoxin fall into five classes: (i) inhibitors of P-glycoprotein efflux transporters increase SDC, such as amiodarone, quinidine, and verapamil; (ii) inducers of P-glycoprotein reduce SDC, such as rifampicin and phenytoin; (iii) reduced intestinal absorption, for example cholestyramine and antacids ; (iv) electrolyte disturbances which sensitise the heart to the current digoxin level, particularly hypokalaemia and hypomagnesaemia; and (v) inhibition of digoxin hydrolysis which is responsible for 15% of digoxin metabolism and is observed with macrolides.

#### 4. Side effect profile and toxicity

Side effects of digoxin include an array of clinical effects including gastrointestinal (nausea and vomiting), neurological (visual disturbances, disorientation), and cardiac (arrhythmias). Despite this, the DIG trial showed little difference in adverse effects leading to withdrawal compared to placebo (3). Digoxin toxicity is a clinical concern resulting from the narrow therapeutic window (0.5 to 0.9 ng/mL). In toxic doses, digitalis precipitates atrial myocardium impulse initiation, AVN block, and an increase in diastolic repolarisation of the AVN (64). Thus digoxin should be avoided in patients with AVN block (unless a permanent pacemaker is in-situ) or Wolff-Parkinson-White Syndrome, where digoxin can increase antegrade accessory pathway conduction due to changes in the AVN refractory period. Digoxin can potentially increase the left ventricular outflow tract gradient in patients with hypertrophic cardiomyopathy, but can be used safely in those without an obstructive phenotype.(65) Patients who develop clinically significant manifestations of digoxin poisoning (i.e. life-threatening arrhythmia, end-organ dysfunction or hyperkalaemia) should be treated with digoxin-specific antibody (Fab) fragments (66).

### **Summary and future perspectives**

Digitalis is a useful therapy in patients with heart failure and those with atrial fibrillation, but there are important practical considerations that complicate its use (**Figure 4**). For patients with HFrEF who have persistent symptoms despite optimal therapy (e.g. ACEi or ARB, beta blocker) digoxin is recommended. In this population there is a reasonable evidence base to indicate no influence on mortality but a reduction in hospital admissions and symptoms. In patients with AF who require rate control, digoxin has yet to be properly investigated in any RCT, with all current recommendations based on conflicting observational studies that are of limited value due to prescription bias. When digoxin is indicated, a low-dose approach is suggested to achieve a serum digoxin concentration <0.9 ng/mL, although the value of digoxin levels in routine clinical practice is unclear. High serum levels do not improve efficacy and yet increase the risk of toxicity and

should be avoided. Practical use of digoxin is often challenging, as patients are typically elderly with renal impairment, polypharmacy and numerous comorbidities.

It has now been 18 years since the last randomised trial of digitalis and there is a clear need for further, adequately powered RCTs to answer important clinical questions about the role of digoxin in clinical practice. Two RCTs are currently underway. The DIGIT-HF trial (Digitoxin to Improve Outcomes in Patients with Advanced Systolic Chronic Heart Failure), is comparing digitoxin versus placebo in HFrEF (NYHA III-IV and LVEF  $\leq$ 40%, or NYHA II and LVEF  $\leq$ 30%) with and without AF (67). The primary outcome is a composite of overall mortality and hospitalisation for worsening HF. The RATE-AF trial (RAte control Therapy Evaluation in Atrial Fibrillation) will enrol permanent AF patients with NYHA Class II and above and randomise them to digoxin or beta-blockers as first-line rate control. The primary outcome is patient-reported quality of life and secondary outcomes include cardiac function, exercise capacity and biomarkers of cellular and clinical effects. Results are expected in 2019 and will form the basis for a future trial assessing the impact of therapy on long-term clinical outcomes in patients with AF (68). Future work is also required to clarify the effect of digoxin concentration and to correlate clinical outcomes with haemodynamic, neurohormonal and electrophysiological changes, in order to inform clinicians about the good and the bad of digitalis use in the 21<sup>st</sup> century.

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O.J.Z. and D.K. drafted the manuscript.

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## **Conflicts of Interest**

O.J.Z. has no competing interests. D.K. reports non-financial support from Daiichi Sankyo, research grants from Menarini, all outside the submitted work; and Lead for the Beta-blockers in Heart Failure Collaborative Group (BB-meta-HF).



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**Table 1. Guidelines on digoxin according to population**

Guideline	Recommendation	Class	Level of evidence
<b>Heart Failure</b>			
American College of Cardiology/American Heart Association 2013 (30)	Digoxin can be beneficial in patients with HFrEF, unless contraindicated, to decrease hospitalisations for HF.	IIa	B
European Society of Cardiology 2012 (22)	Digoxin may be considered to reduce the risk of HF hospitalization in patients in sinus rhythm with an EF $\leq$ 45% who are unable to tolerate a beta-blocker (ivabradine is an alternative in patients with a heart rate $\geq$ 70 bpm).	IIb	B
	Digoxin may be considered to reduce the risk of HF hospitalization in patients with EF $\leq$ 45% and persisting symptoms (NYHA II-IV) despite treatment with an evidence based dose of beta-blocker, ACE inhibitor (or ARB), and an MRA (or ARB).	IIb	B
<b>Atrial Fibrillation</b>			
American College of Cardiology/American Heart Association (46)	In patients with pre-excitation and AF, digoxin should not be administered as it may increase the ventricular response and may result in ventricular fibrillation.	III	B
European Society of Cardiology 2010 (44)	Where monotherapy is inadequate for heart rate control, digoxin should be added. [In pregnancy] if rate control is indicated, and $\beta$ -blockers or non-dihydropyridine calcium channel antagonists are contraindicated, digoxin may be considered.	I	B
	Digoxin is ineffective in converting recent onset AF to sinus rhythm and is not recommended.	III	A
	When pre-excited AF is present, digoxin is contraindicated.	III	C
		III	C
<b>Heart Failure and Atrial Fibrillation</b>			
American College of Cardiology/American Heart Association (46)	<u>AF guidelines:</u> [In AF patients with heart failure] in the absence of pre-excitation, IV digoxin is recommended to control heart rate acutely.	I	B
	[In AF patients] digoxin is effective to control resting heart rate with HFrEF	I	C
	[In AF patients] a combination of digoxin and beta blocker (or a non-dihydropyridine calcium channel antagonist with HFpEF) is reasonable to control resting and exercise heart rate in AF	IIa	B
	Digoxin may be considered to slow a rapid ventricular response with ACS and AF associated with severe LV dysfunction and HF or hemodynamic instability	IIb	C
European Society of Cardiology (22,44)	<u>AF guidelines:</u> [In AF patients with HF] where monotherapy is inadequate for heart rate control, digoxin should be added.	I	B
	If an accessory pathway is excluded, digoxin is recommended as an alternative to amiodarone to control heart rate in patients with AF and acute systolic HF.	I	C
	[In AF patients] digoxin is indicated with heart failure and LV dysfunction, and in sedentary (inactive) patients.	IIa	C
	Intravenous administration of digoxin may be considered to slow a rapid ventricular response in patients with ACS and AF associated with heart failure.	IIb	C
	<u>HF guidelines:</u> [In symptomatic HF (NYHA II-IV), LV systolic dysfunction, persistent/permanent AF and no evidence of acute decompensation] digoxin is recommended in patients unable to tolerate a beta-blocker.	I	B
	[In symptomatic HF (NYHA II-IV), LV systolic dysfunction, persistent/permanent AF and no evidence of acute decompensation] digoxin is recommended as the preferred second drug, in addition to a beta-blocker, to control the ventricular rate in patients with an inadequate response to a beta-blocker.	I	B

ACE, angiotensin converting enzyme; AF, atrial fibrillation; ARB, Angiotensin receptor blocker; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LV, left ventricular; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association.

***Table 2. Meta-analyses reporting clinical outcomes for digoxin versus control***

Study	Studies	Sample size	Population	Study type	Control group	Prospectively registered	Clinical outcomes	Digoxin vs control (95% CI)	Comments
Ziff 2015 (2)	52	621,845	All	RCT and observational (analysed separately)	Placebo/no treatment	Yes	All-cause mortality: Unadjusted observational Adjusted observational Propensity matched observational RCTs Hospitalisation: All-cause Cardiovascular Heart failure related	RR 1.76 (1.57-1.97) RR 1.61 (1.31-1.97) RR 1.18 (1.09-1.26) RR 0.99 (0.93-1.05) RR 0.92 (0.89-0.95) RR 0.92 (0.86-0.97) RR 0.89 (0.85-0.93)	Identified significant relationship between observed mortality with digoxin and study bias. Not able to separate AF patients due to lack of RCTs in this patient group.
Vamos 2015 (39)	19	326,426	AF or HF	RCT and observational	Placebo/no treatment	No	All-cause mortality AF group: all-cause mortality HF group: all-cause mortality	HR 1.21 (1.07-1.38) HR 1.29 (1.21-1.39) HR 1.14 (1.06-1.22)	Non-systematic with arbitrary time period studied and inappropriate meta-analysis of different studies including baseline and time-varying digoxin use.
Chen 2015 (35)	17	408,660	AF	Observational	No treatment	No	All-cause mortality AF + HF: all-cause mortality AF, no HF: all-cause mortality	RR 1.22 (1.15-1.30) RR 1.14 (1.04-1.24) RR 1.36 (1.18-1.56)	Lack of randomised studies. Heart function status not clearly defined in the included studies.
Hood 2004 (36)	13	7,896	HF in sinus rhythm	RCT	Placebo	No	All-cause mortality HF hospitalisation Clinical deterioration	OR 0.98 (0.89-1.09) OR 0.68 (0.61-0.75) OR 0.31 (0.21-0.43)	Restricted to double-blind placebo-controlled RCTs of n ≥20 followed for ≥7 weeks.
Ouyang 2015 (38)	11	318,191	AF	Observational	No treatment	No	All-cause mortality Propensity analysis: mortality AF + HF: all-cause mortality AF, no HF: all-cause mortality	HR 1.21 (1.12-1.30) HR 1.17 (1.13-1.22) HR 1.15 (1.12-1.17) HR 1.18 (1.15-1.21)	Lack of randomised studies. HF not clearly defined in included studies.
Bavishi 2015 (34)	10	76,100	AF plus HF	Observational	No treatment	No	All-cause mortality	RR 1.15 (1.04-1.27)	Lack of randomised studies. HF not clearly defined in included

									studies.
Wang 2015 (40)	8	302,738	AF	Observational	No treatment	No	All-cause mortality AF + HF: all-cause mortality AF, no HF: all-cause mortality	HR 1.38 (1.20-1.57) HR 1.20 (1.07-1.34) HR 1.17 (1.15-1.20)	Lack of randomised studies. HF not clearly defined in included studies.
Hopper 2014 (29)	7	2,987	HF in sinus rhythm	RCT	Digoxin withdrawal	No	Withdrawal of digoxin versus continuation: All-cause mortality All-cause hospitalisation HF hospitalisation	RR 1.00 (0.90-1.12) RR 1.03 (0.98-1.09) RR 1.30 (1.16-1.46)	Only assesses studies of treatment withdrawal in chronic HF patients.
Jaeschke 1990 (37)	7	1,072	HF in sinus rhythm	RCT	Placebo	No	Study withdrawal due to worsening HF	OR 0.28 (0.16-0.49)	Post-hoc primary outcome.

Sorted by sample size. AF, atrial fibrillation; CI, confidence interval; HF, heart failure, HR, hazard ratio; N/S, not stated; OR, odds ratio, RCT, randomised controlled trial, RR, risk ratio.



**Table 3. Dosing and indications of cardiac glycosides**

	<b>Acute digoxin requirement</b>	<b>Chronic digoxin requirement</b>
Clinical indications	Acute heart rate control in AF	Chronic HF symptom control Long-term Rate control for AF
	<b>Digoxin:</b> Total loading dose 0.75-1.5 mg over 24 hours in divided doses given intravenously or orally. <b>Digitoxin:</b> 0.4-0.6 mg intravenous over several minutes	<b>Digoxin:</b> Maintenance dose 0.0625-0.25 mg daily (steady state achieved after 7-10 days; prolonged with renal impairment). <b>Digitoxin:</b> Maintenance dose 0.05-0.3 mg daily.
Loading adjustments	Sensitivity increased by hypokalaemia, hypomagnesaemia, hypercalcemia, hypoxia and hypothyroidism.	
Volume of distribution	Distributed widely (lean tissue and muscle) with large volume of distribution (consider reduced dose in older patients with low muscle mass; patients <45 kg should receive 50% of the normal dose).	
Renal impairment	Reduce loading dose by 1/3 to 1/2 in severe renal insufficiency.	
Concomitant medications	P-glycoprotein efflux transport inhibitors (amiodarone, verapamil) and hydrolysis inhibitors (tetracycline, erythromycin) increase serum digoxin concentration. P-glycoprotein inducers (dexamethasone, phenytoin, rifampicin) reduce serum digoxin concentration. Cholestyramine and antacids reduce digoxin absorption by 25% (patients advised to take digoxin 2 hours earlier).	
Dose adjustment	Dose and serum digoxin concentration have a linear relationship and dose can be altered in proportion to desired concentration (e.g. serum digoxin concentration of 1.6 ng/mL on dose 0.25 mg: if desired concentration is 0.8 ng/mL then dose should be reduced by 50% to 0.125mg).	
Treatment of overdose	Patients who develop clinically significant manifestations of digoxin poisoning (i.e. life-threatening arrhythmia, end-organ dysfunction or hyperkalaemia >5.5 mmol/L) should be treated with digoxin-specific antibody (Fab) fragments. If Fab fragments unavailable, consider atropine for bradycardia (0.5mg intravenous, repeated as needed) and intravenous fluid for hypotension.	

## Figure Legends

### Figure 1. Mechanisms of Digoxin

Upper Left: Digoxin augments parasympathetic tone. Upper right: Digoxin increases the refractory period at the atrioventricular node by reducing the gradient of the pacemaker potential. Lower Left: Digoxin inhibits the sodium-potassium ATPase, increasing intracellular sodium. Calcium is prevented from exiting via sodium-calcium exchanger, raising intracellular calcium, causing further release of calcium from the sarcoplasmic reticulum (calcium-induced calcium-release) leading to a stronger contractile force. Lower right: Frank Starling curves demonstrating the positive inotrope effect.

### Figure 2. The impact of unrecognized bias on treatment effects

Meta-regression of all-cause mortality according to the risk of bias in all studies providing data on rates of death for digoxin versus control (observational and randomized studies). Each circle represents a particular study, with the circle size dependent on precision of each estimate in a random-effects model. Reproduced from Ziff et al, BMJ 2015 (2).

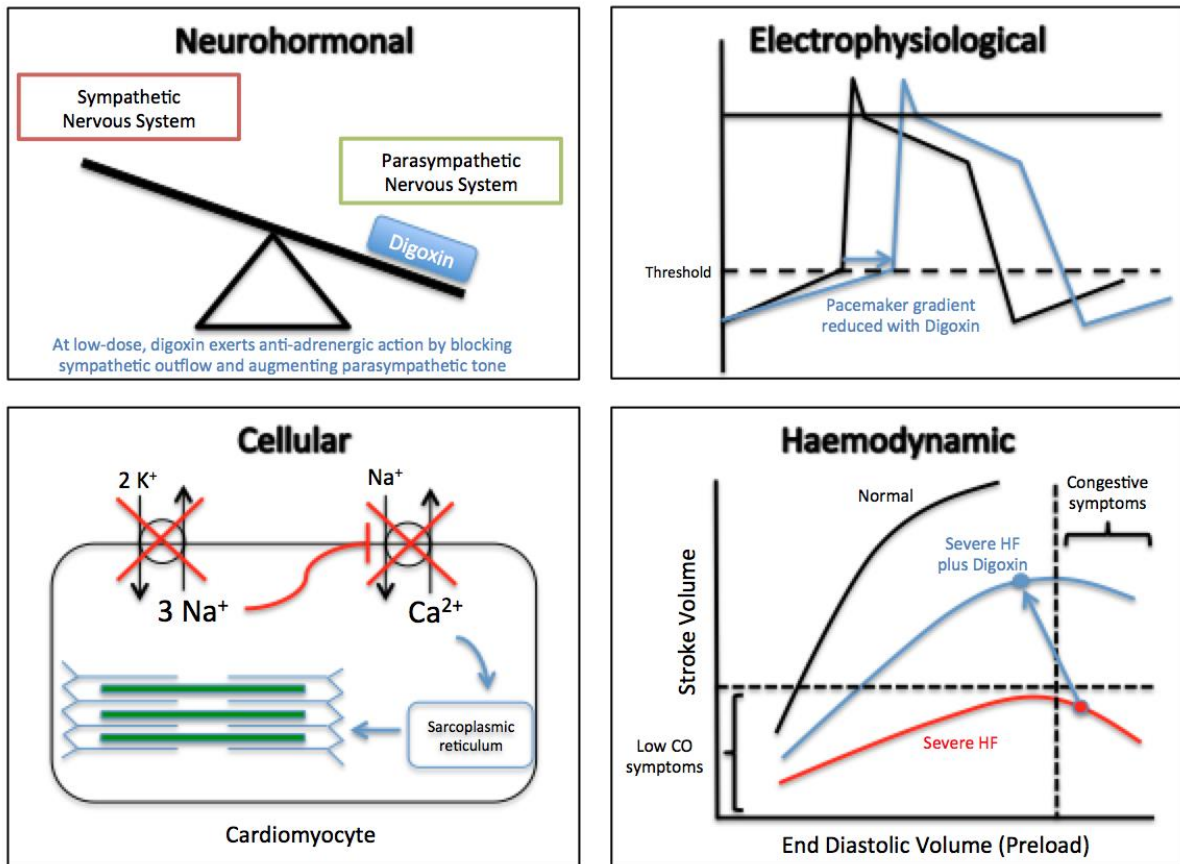
### Figure 3. Digoxin and all-cause mortality in observational and randomised studies

Meta-analyses of all-cause mortality by study design (digoxin versus control therapy). Unadjusted analyses use descriptive statistics for the crude mortality rate. Adjusted analyses use baseline adjustment of some known confounding variables. Propensity-matched analyses utilise a propensity score to match patients for a particular set of baseline covariates. Randomised trials are placebo-controlled. HR, hazard ratio; RR, risk ratio. Adapted from Ziff et al, BMJ 2015 (2).

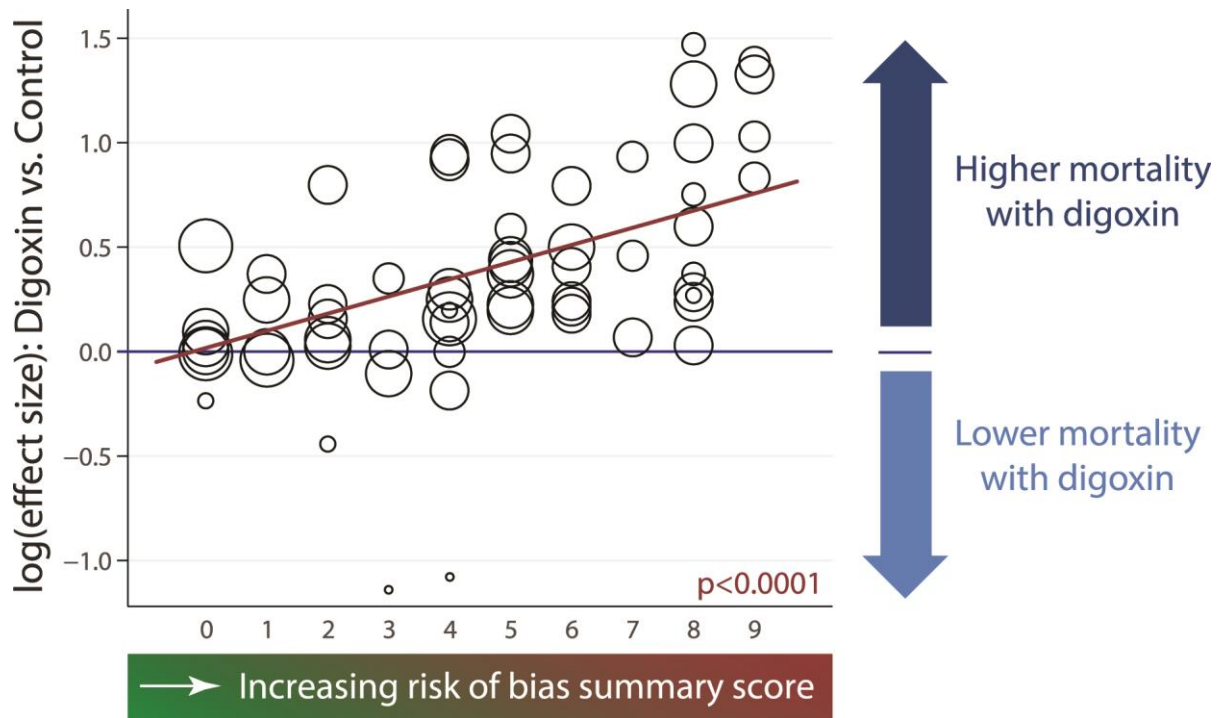
**Figure 4. Pros and cons of digoxin therapy**

Key benefits and concerns of digoxin therapy in patients with atrial fibrillation and/or heart failure.

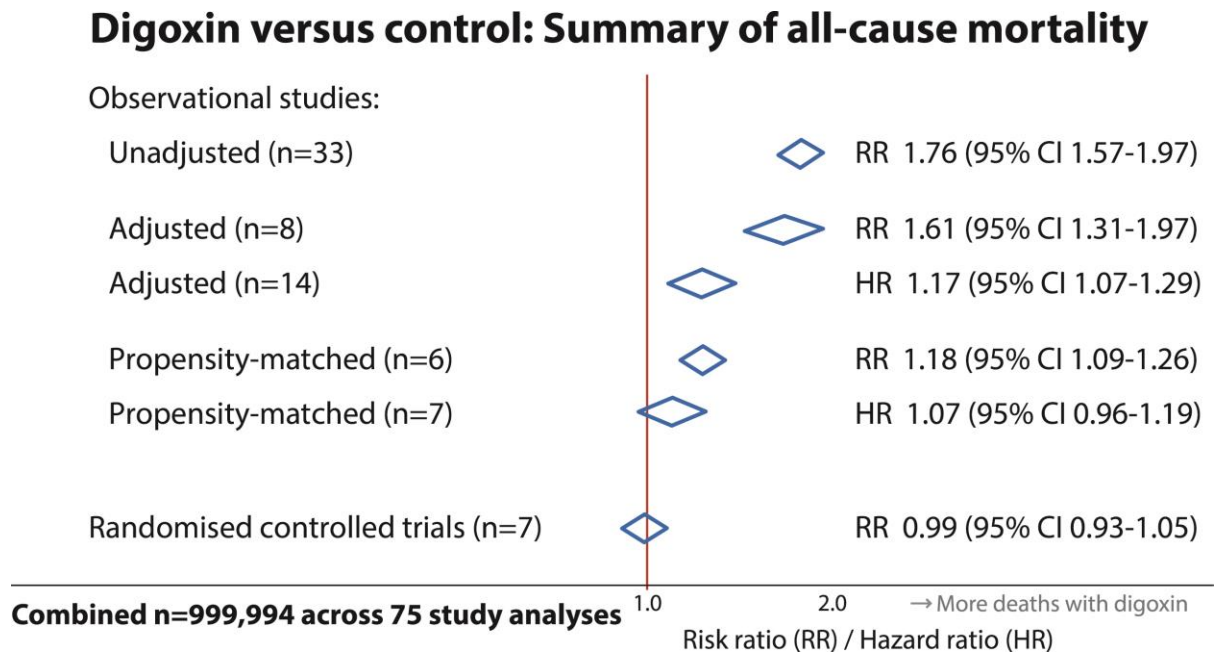
**Figure 1. Mechanisms of Digoxin**



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