# Beta-blockers or Digoxin for Atrial Fibrillation and Heart Failure?

Laurent Fauchier, Guillaume Laborie, Nicolas Clementy and Dominique Babuty

*Department of Cardiology, Trousseau University Hospital and Faculty of Medicine, University François Rabelais, Tours, France*

## Abstract

In patients with atrial fibrillation (AF) and heart failure (HF) with or without systolic dysfunction, either rhythm control or rate control is an acceptable primary therapeutic option. If a rate control strategy is chosen, treatment with a beta-blocker is almost always required to achieve rate control. Adequate ventricular rate control is usually a resting rate of less than 100 beats per minute, but lower resting rates may be appropriate. Non-dihydropyridine calcium channel blockers are often contraindicated when AF is associated with HF with systolic dysfunction. There have been recent debates on a possible reduced efficacy of beta-blockers as well as safety issues with digoxin when treating HF patients with AF. The benefit of beta-blockers on survival may be lower in patients with HF with reduced ejection fraction when AF is present. Digoxin does not improve survival but may help to obtain satisfactory rate control in combination with a beta-blocker. Digoxin may be useful in the presence of hypotension or an absolute contraindication to beta-blocker treatment.

## Keywords

Atrial fibrillation, beta-blocker, digoxin, heart failure

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**Correspondence:** Laurent Fauchier, Service de Cardiologie et Laboratoire d'Electrophysiologie Cardiaque, Centre Hospitalier Universitaire Trousseau, 37044 Tours, France. E: lfau@med.univ-tours.fr

Atrial fibrillation (AF) and heart failure (HF) with or without systolic dysfunction are common cardiac conditions that frequently coexist and share multiple risk factors. HF is a risk factor for AF and AF is a risk factor for HF. Recent studies have focused on the prognostic nature of AF and HF with systolic dysfunction and the questionable use of digoxin and beta-blocker therapy when these conditions coexist. The predominant questions today are whether catheter ablation and rhythm control offer benefit in high-risk patients with AF and HF with or without systolic dysfunction with respect to a reduction in risk of mortality or other 'hard endpoints', and whether more conservative management with drugs for rate control is still an acceptable strategy for many patients. Large randomised multicentre studies are currently ongoing to address these important questions.[1,2]

Only beta-blockers have been shown to improve the prognosis of patients with HF and left ventricular systolic dysfunction, a substantial minority of whom had AF as their baseline rhythm.[3–5] Whether digoxin significantly affects prognosis and mortality in AF associated with HF is poorly known.[6] Furthermore, digoxin does not improve survival of patients with HF who are in sinus rhythm,[7] and long-term therapy with digoxin has been suggested to be a risk factor for death in patients with AF without HF.[8] Among patients with both AF and HF with systolic dysfunction, only a few trials have specifically investigated the use of adding a beta-blocker to digoxin or the opposite.[9,10] In these studies, no comparison was made between beta-blockers alone versus digoxin alone, or the combination. This article reviews the effects of beta-blockers, digoxin and their combination in patients with AF and HF.

## Rate Control in Atrial Fibrillation With Heart Failure

Rate control is a major part of therapy for all patients with AF. Beta-blockers, non-dihydropyridine calcium channel blockers (diltiazem, verapamil) and digitalis are the primary drugs used for ventricular rate control during AF.[11–13] Calcium channel blockers should be avoided in patients with HF. In these patients, regardless of systolic dysfunction, both digoxin and beta-blockers reduce the ventricular rate and both may improve symptoms.

The primary goals of rate control are to improve symptoms and prevent deterioration of cardiac function associated with excessively rapid ventricular rates during AF. In addition, the aims of therapy for rate control are to improve exercise tolerance and quality of life (QoL) and to prevent hospitalisation. In the past, adequate heart rate control had been empirically defined as <80 beats per minute (bpm) at rest. However, the Rate Control Efficacy in Permanent Atrial Fibrillation: a Comparison between Lenient versus Strict Rate Control II (RACE II) study showed that, compared with strict rate control, lenient rate control was not inferior in terms of preventing major clinical events.[14,15] In patients with HF and reduced ejection fraction (EF) from the Swedish Heart Failure Registry, a higher heart rate (HR) was associated with increased mortality in sinus rhythm (SR), but in AF, this was true only for HR >100 bpm.[16] The evidence to support the benefit of HR reduction in improving quality of life and symptoms also remains limited. A study by Jaber et al. analysed the influence of HR (measured by the 6-minute walk test [6MWT] and 24-hour Holter monitoring) on QoL in 89 patients with chronic AF.[17] Jaber et al. found a significant

difference in QoL as measured by physical and mental summary scores in patients with maximal HR ≤110 bpm compared with HR >110 bpm (6MWT), and in the physical summary score in patients with average HR ≤ 80 bpm compared with HR >80 bpm (Holter monitor).[17] Today, it is recommended that treatment for rate control of persistent or permanent AF should aim for a resting HR of <100 bpm.[12,18] In all cases, the HR target may need modification based on the patient's symptoms and preferences.

## Beta-blockers

Beta-blockers are currently a cornerstone in the treatment of patients with HF and reduced EF. The results of pivotal trials have shown a reduction of about one-third in the relative risk of all-cause death with the use of these drugs.[3,4,19] Based on the highest level of evidence, beta-blockers are strongly recommended in clinical European and US guidelines for the management of HF and reduced EF.[20,21] These guidelines state that beta-blockers are indicated in all patients, except those with atrioventricular block, bradycardia and asthma, and recommend use of beta-blockers in patients with HF regardless of baseline rhythm. In AF, beta-blockers are preferred as a rate-control agent in patients after myocardial infarction and in patients with congestive heart failure.[12,22] They may be avoided in patients with chronic pulmonary disease and at risk of bronchoconstriction.[23,24] Of note, carvedilol is a less-potent beta-adrenergic blocking agent compared with metoprolol and is less effective than metoprolol for rate control of AF.[25]

Recent findings have suggested that the effect of beta-blockers on outcome in HF patients with reduced systolic left ventricular ejection fraction (LVEF) who have AF is less than in those who have SR.[26] However, an individual-patient data meta-analysis has shown that beta-blockers reduce mortality risk in patients with HF and reduced LVEF who are in SR but not in those who are in AF.[27] Similar results applied also to cardiovascular death or first hospitalisation for HF.[27] More specifically, treatment effect, judged by reduction in all-cause mortality, seemed to be less in 3066 patients with AF (hazard ratio 0.97, 95 % CI [0.83–1.14]) than in the 13,946 patients not in AF (hazard ratio 0.73, 95 % CI [0.67–0.80]). The results of this analysis suggest that beta-blockers are unlikely to be harmful for AF patients with HF and reduced EF, but the prognostic benefits of beta-blockers have consequently been questioned for patients with HF and AF.

A significant concern is that we have no clear explanation for these recent findings. Clinical experience makes them surprising and counterintuitive although it is possible that our impressions are wrong in evaluating absolute and relative competing risks for the many events in these patients. A rapid ventricular rate in patients with AF is commonly suspected in worsening HF with or without systolic dysfunction (even precipitating hospital admission), whereas control of the ventricular rate in patients with AF seems to improve HF. Beta-blockers are still an effective means of controlling the ventricular rate in patients with AF. In a recent nationwide AF cohort in Taiwan, the adjusted risk of mortality was lower for patients receiving rate-control treatment with beta-blockers.[28] In patients with reduced EF from the Swedish Heart Failure Registry, beta-blocker use was associated with reduced mortality both in SR and in AF.[16] It is thus unclear why beta-blockers would not prevent worsening HF and cardiovascular events in patients with AF. Examination of treatment effect in subgroups is commonly considered with caution, because different baseline characteristics and small numbers of events in subgroups might lead to unreliable conclusions. Additional issues should be addressed, such as the possibility of a drug interaction between digoxin and beta-blocker treatment, unmeasured confounding such as a conduction system disease, expected benefit in patients with previous myocardial infarction, more common use of cardiac resynchronisation therapy and defibrillators nowadays and whether patients with milder symptoms might respond differently to those with more advanced disease. Because most AF patients with HF have a high risk of cardiovascular events, the g eneral view of many clinicians is that the clinical benefit of beta-blockers remains likely, and practice should not change until these questions undergo further evaluation.[29]

## Digoxin

Digoxin and other related cardiac glycosides have been used for more than 200 years for the treatment of HF, and for almost 100 years for heart rate regulation in AF.[30] Since the Digitalis Investigation Group (DIG) study,[7] which demonstrated that whilst digoxin reduced HF hospitalisation there was no significant overall effect on mortality, the place of digoxin in treating HF with systolic dysfunction has steadily declined.[31–34] There remain significant knowledge gaps about how digitalis works and how it should be used in the modern treatment of AF. Studies on digoxin use in patients with AF and the risk of all-cause and cardiovascular mortality have reported rather conflicting results. Whilst digoxin aids HR control in AF, this drug may suffer from a narrow therapeutic index and a potential to contribute to life-threatening ventricular tachyarrhythmias and severe bradyarrhythmias.[35]

Digoxin and cardiac glycosides function by inhibiting the membrane-bound $Na^+/K^+$ ATPase, thereby impeding the transport of sodium from the intracellular to the extracellular space. The resulting loss of the transmembrane sodium gradient decreases the activity of $Na^+/Ca^{2+}$ homeostasis and the increasing intracellular $Ca^{2+}$ concentrations that are thought to lead to the positive inotropic effect of digitalis.[36] In non-cardiac tissue, digoxin acts as a neurohormonal modulator by increasing parasympathetic tone and decreasing activation of the sympathetic nervous system and renin–angiotensin–aldosterone system. Furthermore, in addition to its direct sympatholytic effects at low doses, digoxin indirectly decreases sympathetic outflow by improving carotid sinus baroreceptor sensitivity. Finally, digoxin slows firing at the sinoatrial node and prolongs conduction at the atrioventricular node but has limited electrophysiological effects on the remainder of the conduction system.[37]

Clinically, digoxin may help to control HR in patients with AF without a deleterious decrease in blood pressure. However, digoxin may be less effective, or inadequate, for controlling the ventricular rate during exercise or when sympathetic tone is increased.[38,39] Based on US guidelines,[40] digoxin as a rate control drug is no longer a class 1 indication and is a first-line recommended treatment for management of HR in AF in patients with HF, hypotension or, possibly, in patients who are predominantly sedentary (obviating the need for rate control during activity). As a consequence, digoxin is commonly used by elderly people with a higher risk profile, who are thus expected to have a less favourable prognosis. The Stockholm Cohort of Atrial Fibrillation (SCAF) study showed that digoxin is mainly given to an elderly and frailer subset of patients with AF.[41] When these and other differences in patient characteristics were accounted for, digoxin use appeared to be neutral for long-term mortality in patients with AF.

Some recent observational or post-hoc analyses found an increased mortality among digoxin-treated patients. The Registry of Information

and Knowledge about Swedish Heart Intensive Care Admissions (RIKS-HIA) examined 1-year outcomes in patients on digoxin with AF, congestive HF with reduced or preserved EF, or both, by comparing them with a matched group of patients who were not receiving digoxin.[8] Overall mortality was significantly higher in the 4426 digoxin-treated patients with AF and no history of HF compared with 16 587 controls at discharge (hazard ratio 1.42, 95 % CI [1.28–1.56]). No such difference was seen in patients with HF. Although this study included a large number of patients, it was performed in an intensive care setting, which makes it difficult to translate the results into other clinical settings.

A substudy from the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial reported that in patients with AF, digoxin was associated with increased all-cause mortality after controlling for comorbidities and propensity scores, regardless of the presence or absence of underlying HF.[42] In this study, digoxin was used as a time-dependent covariate in a Cox proportional hazard model. Patients changed from being in the 'on-digoxin' group to the 'not on-digoxin' group if their medication use changed during the study, and their associated time at risk for death contributed to each respective group. However, another study from AFFIRM, by Gheorghiade et al., which employed a propensity-matched analysis, did not reveal a difference in all-cause mortality.[43] Digoxin use was there assessed at a fixed time point only, at the time of randomisation. Another post-hoc analysis from the AFFIRM study[44] even suggested that digoxin may play a beneficial role in patients with AF and significant left ventricular dysfunction as part of a rate control strategy, adding questions to the general confusion with recent very conflicting reports.[34, 46–48] A plausible explanation of digoxin-associated higher mortality in the post-hoc analysis from the AFFIRM study by Whitbeck et al. is the use of digoxin as a time-dependent treatment variable. The effect of a time-dependent treatment on survival may only be valid in situations where the changes in treatment over time are random and are not related to health deteriorations.[49,50] Another major limitation in the article by Whitbeck et al. is that age was not used as a covariate to generate the propensity score. Digoxin is mainly given to elderly people, with older age obviously being associated with an increased mortality. Medication interaction may also play a role in these patients. In the Permanent Atrial fibriLLAtion Outcome Study Using Dronedarone on Top of Standard Therapy (PALLAS) trial, there was a strong effect of concurrent digoxin use on the adverse effect of dronedarone on cardiovascular death.[52]

In 1269 consecutive patients with both AF (permanent or non-permanent) and HF (preserved or reduced LVEF), we found, after thorough adjustment on baseline characteristics, that treatment with beta-blocker alone or with beta-blocker plus digoxin was associated with a similar decrease in the risk of death. Digoxin alone was associated with a similar (and not worse) survival to that of patients without any rate control treatment.[52] More generally, it was found in a recent meta-analysis of observational and controlled trial data that digoxin was associated with a neutral effect on mortality in randomised trials and a lower rate of admissions to hospital across all study types.[53]

Digoxin has minimal pro-arrhythmic effects when dosed to achieve the therapeutic serum drug concentration (SDC). By contrast, at a supratherapeutic SDC or therapeutic SDC with concomitant hypokalaemia, atrioventricular block and escape rhythms are electrocardiographic manifestations of toxicity. Overall, the relationship between digoxin effect and/or toxicity and drug concentrations is poorly defined, and measuring concentrations to assess drug effect (as opposed to true toxicity) has unclear benefit. However, the results from a post-hoc study conducted by Rathore et al. suggest that the effectiveness of digoxin in the DIG trial varied according to patients' serum drug concentrations.[35] An SDC of 0.5–0.8 ng/ml would likely constitute the optimal therapeutic range for digoxin, and another study from AFFIRM found that 2 ng/ml or higher may be harmful. Moreover, although digoxin improves the overall neurohormonal profile in severe HF at low doses, it has been suggested that further dose increases within the therapeutic range have no added neurohormonal benefit and may in fact have a sympathetic action.[54] These findings may suggest that the serum concentration of digoxin could be a determinant of clinical events.[55–57] In the AFFIRM trial, an SDC ≥1.0 ng/ml was encouraged and higher doses of digoxin were used to meet the stringent rate control requirement (resting HR of <80 bpm and exercise heart rate <110 bpm), which might not be the case in everyday clinical practice.

## Perspectives for Future Investigation

To date, there is no clear information on the benefit of beta-blocker and/or digoxin treatment in subgroups of patients with HF and AF (whether permanent or non-permanent), with HF and decreased or preserved systolic HF, or with the ischaemic or non-ischaemic aetiology associated with the disease. Most current knowledge about digoxin use in AF comes from observational cohorts and not from randomised trials.[7] By contrast, only limited observational data are available from everyday clinical practice regarding the events and possible benefits associated with beta-blocker use in patients with AF and HF.[52] From an ethical perspective, it might be difficult today to carry out a large randomised trial with digoxin for rate control, as there are other adequate treatments. Several studies have performed propensity score analysis in order to increase the comparability of patient characteristics between digoxin-treated and untreated patients.

Even with sophisticated statistical techniques, it may be challenging to fully adjust for disease severity and the indication for treatment as assessed by the provider. Thus, the association between digoxin and/or beta-blocker use and mortality may still be wrongly estimated. This is due to unknown or unmeasured potential residual confounders, particularly those related to severity of HF, symptoms, haemodynamic status and general side-effects, all of which should be better characterised in future adjusted observational studies. Reporting non-randomised, 'real-world' registry data from large cohorts of consecutive patients recruited with AF may be relevant in that these data are complementary to the data possibly reported in randomised clinical trials, which are unlikely to be reinitiated. Observational studies may be of value because they shed light on the use of competing treatment options in current practice and because they include patients at high risk who are frequently not represented in clinical trials.

Another limitation in many studies is that information about patients' exposure to digoxin and beta-blockers is most often fragmentary. Medication changes during follow-up are not recorded in many observational studies. Similarly, the compliance with digoxin or beta-blocker therapy, and whether it relates to clinical events, should be better characterised in future analyses. Finally, HR is difficult to fully describe in any analysis with AF patients and presents a field of investigation. This may help to establish whether the best target for an optimal rate control strategy is HR during AF episodes,

or alternatively HR in SR for patients with non-permanent AF, whether it is mean HR or maximum HR, or possibly HR above a given limit for a given duration, both of which need to be determined.

Some ongoing randomised clinical trials may help to answer these questions in AF patients with HF, such as the Randomized Ablationbased Atrial Fibrillation Rhythm Control Versus Rate Control Trial in Patients With Heart Failure and High Burden Atrial Fibrillation (RAFT-AF) trial, which will test the hypothesis that restoration of SR is superior to rate control in patients with AF and HF with either impaired or preserved LV function. More generally with respect to perspective for future investigations, the serious limitations of observational cohort studies in improving or understanding the benefit versus the risk of digoxin or beta-blockers in AF patients with HF advocate for smaller, but blinded and randomised studies to assess their potential benefits on wellbeing, exercise tolerance and QoL, which are the primary reason to administer drugs in this setting.

## Conclusion

Based on values and preferences, rate control therapy most often includes a beta-blocker, but should be individualised on the basis of the type and severity of underlying structural heart disease, the activity level of the patient and other individual considerations. Digoxin is mainly given to elderly AF patients with HF and impaired LV function. Consequently, its use is associated with increased crude rates of mortality in observational analysis.[58] Once differences in patient characteristics have been accounted for, it is unclear whether digoxin has a clear independent association with increased mortality. Although these results are from moderate-quality evidence only, one may suggest that digoxin should not be used as the initial therapy for active patients. Rather, it should be reserved for rate control in AF patients who are sedentary or who have left ventricular systolic dysfunction, particularly when beta-blockers do not achieve sufficient rate control and when they are poorly tolerated or contraindicated. ■


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