

# Conversion of atrial fibrillation to sinus rhythm and rate control by digoxin in comparison to placebo

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**Aims** A randomized, double-blind study with a high dose of digoxin administered intravenously for conversion of atrial fibrillation (not due to haemodynamic alterations) to sinus rhythm, and for rate control in converters and non-converters was set up. Outcome measures were conversion within 12 h; time to conversion; early rate control; and stable slowing within 12 h.

**Methods** We studied 40 patients with recent onset (<1 week) atrial fibrillation; controls received saline intravenously, the other patients digoxin 1.25 mg.

**Results** One patient converted before digoxin administration. Conversion occurred in 9/19 patients on digoxin and in 8/20 on placebo (ns). The mean time to conversion tended to be shorter only for digoxin. Two late conversions on placebo were observed within 24 h. Heart rate during

atrial fibrillation decreased after 30 min for converters and non-converters ( $P<0.05$ ). For all patients on digoxin, heart rate after 30 min was lower compared to baseline ( $P<0.002$ ) and to placebo ( $P<0.02$ ). Persistent, stable slowing occurred only in 3/10 non-converters on digoxin ( $P<0.05$ ), and two patients developed bradyarrhythmias. QTc was shortened immediately after conversion in all patients. Converters had baseline characteristics similar to those of non-converters.

**Conclusions** Intravenous digoxin offers no substantial advantages over placebo in recent onset atrial fibrillation with respect to conversion, and provides weak rate control. (Eur Heart J 1997; 18: 643–648)

**Key words:** Arrhythmias, atrial fibrillation, bradycardia, digoxin, heart rate, QT interval.

## Introduction

Acute and paroxysmal atrial fibrillation are very common arrhythmias. Both forms can cause disabling symptoms, and carry a risk for systemic embolism if they are not converted to normal sinus rhythm<sup>[1,2]</sup>. It remains unclear which is the optimum treatment for conversion of atrial fibrillation of recent onset<sup>[3–5]</sup>. Cardioversion with direct current requires general anaesthesia, and therefore drug treatment remains the first option if no haemodynamic instability is present. Oral or intravenous digoxin is used widely for this arrhythmia, despite some evidence that it offers no major advantage over placebo therapy<sup>[6]</sup>. Antiarrhythmic class I drugs (at least in the intravenous form) are certainly more active than digoxin, but seem to be more risky, at least in patients who are haemodynamically compromised, or who have underlying ischaemic heart disease<sup>[3,7,8]</sup>. Therefore, therapy

with digoxin should be assessed, as it is used in patients with concomitant heart failure<sup>[9,10]</sup>, and is believed to lower the ventricular response in atrial fibrillation.

The aim of our study is to assess whether digoxin in a dose higher than previously studied is more effective than placebo with regard to cardioversion, and whether it significantly lowers the ventricular rate<sup>[6]</sup>. We also attempted to analyse whether it would be possible to recognize 'converters' (those who respond, or who spontaneously convert to sinus rhythm) and 'non-converters' (those who do not convert), in order to give this group other antiarrhythmic drugs at an earlier stage. As evidence exists that the autonomic system plays a very important role in the pathogenesis of atrial fibrillation, and its conversion to sinus rhythm we also assessed the evolution of the heart rate and the QT interval in converters<sup>[11]</sup>.

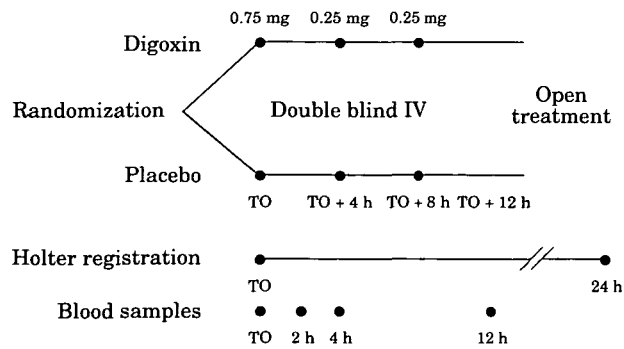
## Methods

### Patients

Patients were eligible for this study if they had symptomatic atrial fibrillation of recent onset (defined as

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**Figure 1** Flow chart of the study. IV=intravenously; TO=start of drug infusion.

present less than one week, as judged from the clinical history or documented with electrocardiography). The ventricular rate had to be more than 100 beats  $\cdot$  min<sup>-1</sup> on the first recording. Patients were excluded from the study if treatment with cardiac glycosides had been given within the last week, or if antiarrhythmic drugs had already been used in the last 72 h. Other contraindications were previous use of amiodarone, the clinical setting of acute myocardial infarction or recent coronary artery bypass grafting, and haemodynamic or respiratory instability. Electrolyte disturbances were also excluded. No patients with atrial flutter were included. Approval of the Ethics Committee was obtained. All patients were fully informed of the investigational approach, and gave their consent.

### Treatment

Digoxin and placebo were provided in identical ampoules, prepared by the Laboratory of Pharmaceutical Technology of the Faculty of Pharmaceutical Sciences of the University of Ghent (Ghent, Belgium). The digoxin ampoules contained 0.50 mg of digoxin, and the placebo ampoules contained normal saline, both in a volume of 2 ml. The schedule and the dosage of the double-blind randomized drug administration is presented in Fig. 1. A total amount of 1.25 mg digoxin was given. It was intended to give the full dosage, even if conversion to sinus rhythm occurred. The initial dose of digoxin was infused over 10 min, the subsequent 0.25 mg doses over 5 min. Verapamil was allowed if there was no lessening in the rapidity of the heart rate. Other pharmacological antiarrhythmic treatment was allowed after the initial 12 h. If atrial fibrillation persisted 24 h after the start of the digoxin administration, electrical or chemical cardioversion were proposed to the patient, depending on the clinical situation.

### Monitoring

Digoxin levels were checked at baseline, and after 2, 4 and 12 h. A 24-h electrocardiographic recording was

used to document the heart rate, and the moment of conversion. Most patients were additionally monitored, but this was not a requirement. The Holter tapes were analysed after visual inspection and editing by an experienced technician. Average heart rates were calculated over 1 min time periods, using software developed by Elatec (Ela Medical, France). 'Stable slowing' of the ventricular rate was assessed on 6 min intervals. QT analysis was performed with investigational software, automatically calculating the QT interval from the beginning of the QRS complex to both the apex (QTa) and the end of the QT interval (QT<sub>e</sub>). The mean value of RR and QT over 30 beats was taken at each point, and the Bazett formula was used for correction.

### Endpoints

The primary endpoints were conversion to sinus rhythm within 12 h of treatment initiation. To analyse ventricular response, the average ventricular rates (1 min intervals) were compared between digoxin and placebo groups, beginning 10 min after the initiation of therapy. Further analysis was also performed on the rates immediately before and after conversion. Rates before conversion were also compared to rates of non-converters at comparable time intervals. Heart rates were only compared if the basic rhythm was similar (atrial fibrillation or sinus rhythm). A secondary endpoint was the achievement of stable ventricular slowing (heart rates <100 beats  $\cdot$  min<sup>-1</sup>) within 6 to 12 h.

### Statistical analysis

Values are expressed as means and standard deviations. Non-parametric tests were used for comparison. *P* values <0.05 were considered to be significant.

## Results

### Subjects

A total of 40 patients were randomized. One patient assigned to the digoxin group converted to sinus rhythm before any treatment was given. Further results relate to the remaining 39 patients (23 males and 16 females). The mean age was 64  $\pm$  17 years. The average body weight was 73  $\pm$  14 kg. The average duration of the episode of atrial fibrillation was 32  $\pm$  37 h (range 1–120). In 12 patients no cardiovascular disease could be identified, and atrial fibrillation was considered idiopathic. The mean initial heart rate was 143  $\pm$  28 beats  $\cdot$  min<sup>-1</sup>. A total number of 20 patients received placebo, and 19 received digoxin treatment. Only one patient received verapamil during the observation. No significant differences were observed in the baseline characteristics of the two treatment groups (Table 1).

**Table 1** Baseline characteristics of treatment groups

	Total group	Placebo	Digoxin
Number	39	20	19
Age (years)	64 ± 17	67 ± 9	61 ± 22
Gender (male/female)	23/16	13/7	10/9
Body weight (kg)	73 ± 14	73 ± 12	73 ± 17
Idiopathic (n)	12	6	6
Initial heart rate (beats · min <sup>-1</sup> )	144 ± 28	145 ± 28	143 ± 28
Duration (h)	32 ± 37	15 ± 21	49 ± 43

Means ± standard deviation.

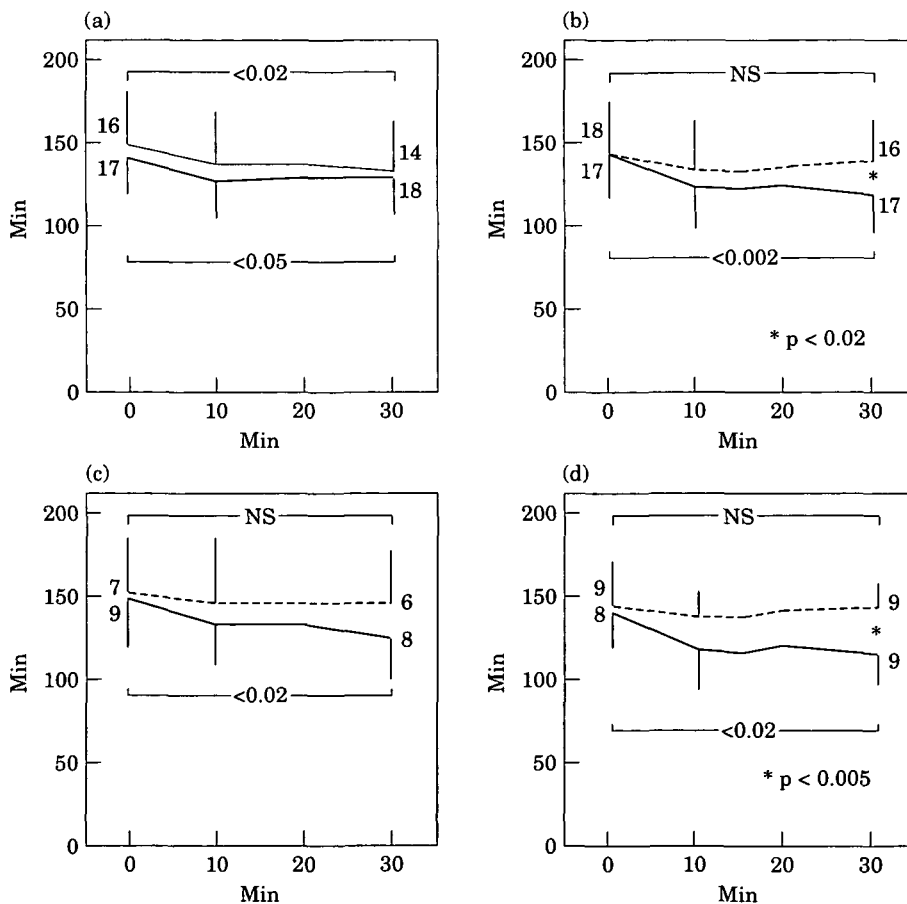
### Conversion with digoxin or placebo

Seventeen patients (43.6%) converted within 12 h, nine of whom received digoxin and eight placebo (47.4% and 40% of each group). The average time to conversion for digoxin was 81 ± 53 min (range 38 to 177 min), and 183 ± 224 min (range 3 to 596 min) for the eight early

converters on placebo (ns). Two patients on placebo converted without additional intervention to sinus rhythm after the 12 h observation period (after 855 and 959 min). The total percentage of converters on placebo during the period of 24 h therefore becomes 50%.

### Evolution of ventricular rates after initiation of digoxin or placebo treatment

Heart rate trends (1 min average) according to the administered therapy and response groups are shown in Fig. 2. The initial mean heart rate in all patients was 143 ± 28 beats · min<sup>-1</sup>. Ten minutes after initiating treatment, it decreased to 128 ± 27 beats · min<sup>-1</sup>. For those receiving digoxin the heart rate became 123 ± 27 beats · min<sup>-1</sup>; for placebo 133 ± 28 beats · min<sup>-1</sup> (ns). After 30 min the heart rate was 128 ± 25 beats · min<sup>-1</sup> for the total group, significantly different from the initial heart rate ( $P < 0.005$ ). In those patients receiving digoxin, it fell to 118 ± 23 beats · min<sup>-1</sup> ( $P < 0.002$ ); for placebo,



**Figure 2** Evolution of heart rate (mean with standard deviation) vs time in different categories over the first 30 min after intravenous therapy was initiated. (a) Heart rate according to outcome (--- = non-converters, — = converters); (b) heart rate according to treatment group (--- = placebo, — = digoxin); (c) converters and treatment (--- = placebo, — = digoxin), (d) non-converters and treatment (--- = placebo, — = digoxin). Numbers indicate the patients remaining in the subgroups.

**Table 2 Heart rate before and after conversion (beats . min<sup>-1</sup>, averaged over 1 min)**

	Total group	Placebo	Digoxin	
Number	17	8	9	
Heart rate				
1 min before	134 ± 27	134 ± 23	131 ± 31	ns
1 min after	104 ± 32	96 ± 23	111 ± 36	ns
1 h after	91 ± 17	88 ± 18	95 ± 15	ns

Means ± standard deviation.

it remained 139 ± 33 beats . min<sup>-1</sup> (ns from baseline). At 30 min mean heart rates on digoxin were lower than on placebo ( $P < 0.02$ ). In the converters no differences existed in the heart rates (during atrial fibrillation) between either treatment group. Converters on digoxin had lower heart rates at 30 min than at baseline. For non-converters treated with digoxin, in comparison to placebo therapy, a slower heart rate was observed not only at 30 min ( $P < 0.005$ ) but also after 2 h ( $P < 0.03$ ). Digoxin also slowed heart rates from baseline to 30 min in the non-converting group ( $P < 0.02$ ).

### Evolution of ventricular rates and QT intervals in converters before and after conversion

Heart rate analysis in converters in the minute immediately before and after conversion, showed that digoxin did not play an important role in the control of ventricular rate in this particular situation (Table 2). Patients on digoxin had a ventricular rate of 131 ± 31 beats . min<sup>-1</sup> the minute before conversion, as opposed to 134 ± 23 beats . min<sup>-1</sup> for patients on placebo (ns). The total converting group had a rate of 104 ± 32 beats . min<sup>-1</sup> immediately after the conversion, decreasing to 91 ± 17 beats . min<sup>-1</sup> after 1 h ( $P < 0.05$ ). The digoxin group had a heart rate of 95 ± 15 beats . min<sup>-1</sup> after 1 h ( $P < 0.1$  compared to the rate after conversion), and the placebo group had a rate of 88 ± 18 beats . min<sup>-1</sup> ( $P < 0.07$  compared to the rate after conversion).

No additional information was gained from analysis of average RR, QTa and QTe intervals and corresponding QTc intervals before and after conversion with digoxin or placebo, as the subgroups became too small. However, the corrected QTe (QTEc) immediately after conversion was significantly shorter (372 ± 47ms) than immediately before conversion (413 ± 48ms), and within 5 min returned to its earlier values.

### Conversion during further follow-up and secondary endpoints

Persistent, stable slowing of the heart (<100 . min<sup>-1</sup>), was uncommon in non-converting patients, and occurred only in 3/10 patients on digoxin ( $P < 0.05$ ). During

the second 12 h of the observation period, additional antiarrhythmic drug treatment was given to 14 of the 20 patients (a cibenzoline protocol was used). This resulted in conversion of six more episodes. No benefit or disadvantage was observed in this respect for the digoxin patients (three of the six converters; six of the eight non-converters). This brings the total number of cardioverted patients to 26 (65%) of the initial group of 40 within 24 h.

### Side effects

One patient on digoxin developed symptomatic sinus arrest within 1 h after achievement of sinus rhythm. The digoxin level at 2 h (57 min before conversion) was 1.87 ng . ml<sup>-1</sup>. Another patient developed asymptomatic pauses up to 3.05 s immediately after conversion to sinus rhythm. One patient on digoxin converted after 116 min, but had recurrent atrial fibrillation 11 h later. One patient had hypotension during additional antiarrhythmic treatment.

### Differences between converters and non-converters

No differences in age, sex, body weight, clinical variables, or initial heart rate were observed between converters and non-converters (Table 3). The duration of atrial fibrillation was also similar for both groups. The mean maximal digoxin plasma level in the converters on digoxin was 2.9 ± 1.8 ng . ml<sup>-1</sup>, while the mean maximal level in the group of non-converters was 3.3 ± 1.7 ng . ml<sup>-1</sup> (ns). When heart rates were assessed at 30 min after therapy was initiated, converters were not different from non-converters. If we only analysed patients on placebo, heart rate at 30 min was 149 ± 26 beats . min<sup>-1</sup> for converters, while it was 139 ± 18 beats . min<sup>-1</sup> for non-converters (ns). If we consider the digoxin group, converters had a heart rate of 123 ± 26 beats . min<sup>-1</sup> where non-converters had a rate of 114 ± 20 beats . min<sup>-1</sup> (ns). Further analysis of heart rates during atrial fibrillation in the minute before conversion with heart rates at comparable time intervals for matched non-converters showed no significant differences, with only a tendency to faster rates for converters on digoxin ( $P < 0.1$ ).

### Discussion

It has been suggested that digoxin is highly effective for termination of atrial fibrillation<sup>[12]</sup>. The time course of conversion after digitalis administration has been used as an argument to prove the efficacy of the drug<sup>[12]</sup>. However, our study shows that digoxin is not very effective for the conversion of atrial fibrillation of recent onset, and in this regard supports the findings of Falk

Table 3 Comparison of converters and non-converters

	Total group	Converters	Non-converters	
Number	37	17	20	
Age (years)	64 ± 17	60 ± 22	67 ± 10	ns
Gender (Male/female)	21/16	8/9	13/7	ns
Body weight(kg)	73 ± 14	72 ± 14	73 ± 15	ns
Idiopathic	12	5	7	ns
Heart rate (beats . min <sup>-1</sup> )	144 ± 28	148 ± 13	141 ± 24	ns
Duration (h)	42 ± 58	39 ± 72	43 ± 42	ns
Maximal digoxin (ng/ml)*		2.9 ± 1.8	3.3 ± 1.7	ns
2 h digoxin (ng/ml)*		2.8 ± 1.7	3.7 ± 3.1	ns

\*Only for patients with digoxin treatment. Means ± standard deviation.

*et al.*<sup>[6]</sup>. It appears that hospitalization with bed rest (i.e. placebo) is just as effective as a high dose of intravenous glycosides, resulting in about 50% conversion within a reasonable time. These findings have implications for any future investigation directed towards cardioversion.

However, some questions concerning the role of digoxin in rate control in atrial fibrillation remain unanswered. Falk provided no data on the effect of digoxin on ventricular rate in recent onset atrial fibrillation. Digoxin is considered to be effective for rate control<sup>[13]</sup>. Recurrent paroxysms were even associated with faster conduction if digoxin was given<sup>[14]</sup>. It is certain that digoxin does not control ventricular rate during exercise<sup>[15]</sup>. Furthermore, additional drugs to block atrioventricular nodal conduction were often prescribed in trials designed to convert with digoxin<sup>[16]</sup>. Our data on rate and slowing in converters and non-converters (in this population without overt heart failure) support the idea that digoxin actually lowers the ventricular rate. The effect is visible very early after initiation of therapy, and could be explained by an early vagotonic effect on the atrioventricular node<sup>[17]</sup>. This rate control is not impressive, and it is striking that converters tended to have faster ventricular rates before they converted. This suggests that sympathetic tone and activation become more important. The fact that the QTc interval is shortened in the first minute after conversion (in the entire converting group) is further evidence for sympathetic activation (or vagal withdrawal) at this moment. It is shown that drugs, commonly used for rate control, sustain atrial fibrillation<sup>[18]</sup>.

Stable heart rate slowing (when conversion does not happen) is more common with digoxin, but only in a small proportion of patients. Heart rates remained too fast to be considered clinically acceptable, and further steps are to be taken to convert patients, rather than to slow rates when atrial fibrillation persists.

One important variable in predicting the achievement of a stable sinus rhythm with drug treatment is a short duration of fibrillation (this was similar in both our treatment groups) and the absence of organic heart disease (advanced heart disease was only detected in a minority of patients in both groups)<sup>[16,19]</sup>. The advantage of chemical cardioversion is that general anaesthesia can be avoided. However, early electrical cardio-

version (within 24 h) seems indicated in some patients, when after an initial phase of bed rest, and administration of the initially selected drug, atrial fibrillation remains present.

Digoxin should not be considered for conversion of atrial fibrillation when no overt left ventricular failure accompanies atrial fibrillation<sup>[20]</sup>. Other additional, necessary interventions make treatment with digoxin (as first choice) more expensive for the treatment of atrial fibrillation than one would expect<sup>[16]</sup>. Furthermore, its efficacy in rate control is only limited, even in this dosage. High intravenous doses are associated with bradyarrhythmias after conversion.

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