Title: **Efficacy and safety of digoxin in patients with heart failure and reduced ejection fraction according to diabetes status: An analysis of the Digitalis Investigation Group trial (DIG).**

Short Title: Digoxin, HF-REF and diabetes.

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Disclosures: The study was not supported by any public grant or industry support.

Word count: 4945 (all-included)

ABSTRACT

Background: Digoxin is recommended in symptomatic heart failure patients with reduced ejection fraction (HF-REF) in sinus rhythm and refractory to other evidence-based therapy. Although HF-REF patients with diabetes have worse functional status than those without, the effects of digoxin have not been specifically evaluated according to diabetes status.

Methods: We examined the efficacy and safety of digoxin in HF-REF patients with and without diabetes in the Digitalis Investigation Group trial. Mortality from all-cause, cardiovascular (CV) causes and heart failure (HF), along with HF hospitalisation and suspected digoxin toxicity were analyzed according to diabetes status and randomised treatment assignment.

Results: Of the 6800 patients, those with diabetes (n=1933) were older, more often women, had worse clinical status and more co-morbidity than those without diabetes. All-cause and CV mortality were higher in patients with diabetes than in those without and digoxin did not reduce mortality in either sub-group. The rate of HF hospitalisation (per 100 person-years) in patients with diabetes was higher than in those without and was reduced by digoxin in both patient groups: diabetes - placebo 20.5 and digoxin 16.0 (HR 0.79, 95%CI: 0.68-0.91); no diabetes - placebo 12.7 and digoxin 8.7 (HR 0.69, 0.62-0.77); interaction p=0.14. Suspected digoxin toxicity in patients randomised to digoxin was more common among patients with diabetes than without (6.5% versus 5.8%), as was hospitalisation for digoxin toxicity (1.4% versus 0.8%).

Conclusion: Added to an ACE inhibitor, digoxin reduced HF hospitalisation in HF-REF patients with and without diabetes without a substantial risk of toxicity.

Keywords: digoxin; heart failure; diabetes; outcome

1. INTRODUCTION

Heart failure patients with diabetes have more co-morbidity and worse functional status than without diabetes.[1-5] Patients with diabetes also have much higher rates of adverse cardiovascular outcomes. [1-5] Consequently, there is a particular need for treatments that improve symptoms, functional capacity and morbidity/mortality outcomes in heart failure patients with diabetes.

Although digoxin is the oldest of currently recommended therapies for heart failure, its effects in patients with diabetes have never been described. This omission is important as digoxin is often reserved for patients with worse heart failure status and such patients are more likely to have diabetes (as outlined above).[6,7] Patients with diabetes are also more likely than those without to have renal dysfunction, potentially increasing the risk of digoxin toxicity. [1-5] We have, therefore, examined the efficacy and safety of digoxin in heart failure patients with and without diabetes randomised in the Digitalis Investigation Group trial (DIG).[8.9]

2. METHODS

2.1. DIG inclusion and exclusion criteria

The rationale, design and results of DIG have been published.[8, 9] Patients were randomised at 302 clinical centers in the United States and Canada. The study was approved by the ethics committee at each participating center and all patients gave written informed consent.

Patients were eligible if they had heart failure and a left ventricular ejection fraction (LVEF) of 45% or less and were in sinus rhythm. The diagnosis of heart failure was based on current or past clinical symptoms (limitation of activity, fatigue, and dyspnoea or orthopnoea), signs (edema, elevated jugular venous pressure, rales, or a gallop rhythm), or radiologic evidence of pulmonary congestion. Exclusion criteria included a serum potassium below 3.2 mmol/l or above 5.5 mmol/l and significant renal insufficiency (creatinine greater than 3.0 mg/dl) or severe liver disease. Investigators were strongly encouraged to give study patients an angiotensin-converting–enzyme inhibitor.

2.2. Study drug randomization and dosing and trial outcomes

Patients were randomly assigned to receive digoxin or placebo. The initial dose of study drug was determined using an algorithm which took account of patient age, sex, weight, and renal function.[8] Investigators were permitted to modify dose of study drug based on other factors, such as use of concomitant drugs that might alter digoxin pharmacokinetics.

Follow-up visits took place at 4 weeks and 16 weeks after randomisation and every 4 months thereafter. The primary outcome was mortality. The secondary outcomes were mortality from cardiovascular causes, death from worsening heart failure, hospitalisation for worsening heart failure, and hospitalisation for other causes, in particular suspected digoxin toxicity. The composite outcome of cardiovascular death or heart failure hospitalisation was examined in the present study as a more contemporary endpoint in heart failure trials.[10-13]

2.3. Diabetes status

The DIG trial was a large, simple, National Institutes of Health (NIH) funded study with limited biochemical investigations which did not include haemoglobin A1c (HbA1c) or fasting or non-fasting glucose. Thus, a diagnosis of diabetes is based on a "Yes/No" checkbox under medical history in the study case report form. There were no specific diagnostic criteria for diabetes - the diagnosis was as reported by investigators.

2.4. Statistical analysis

We have full access to the annonymised individual patient's data. Descriptive statistics were used to compare patients with and without diabetes. Data are presented as means (standard deviation [SD]) or medians (inter-quartile range [IQR]) for continuous variables and frequency (percent) for categorical variables. We examined the effect of randomised treatment on the following major clinical outcomes: the composite of cardiovascular (CV) death or heart failure (HF) hospitalisation (as the most commonly used composite in contemporary HF trials); the composite of HF death or HF hospitalisation (as pre-specified in the DIG trial protocol); the components of these composites; and all-cause death (the pre-specified primary endpoint in the DIG trial protocol). Comparison of clinical outcomes between study groups was performed using Kaplan-Meier estimates, with log-rank test, and a supportive Cox proportional-hazards regression model to calculate hazard ratios and 95% confidence intervals. The interaction between diabetes and the effect of treatment was also examined for each clinical outcome. The number of hospital admissions (taking account that individual patients had repeat admissions) in the study groups was evaluated using a negative binomial model.

We examined serum digoxin concentrations, creatinine and potassium in the study groups. We also explored the presence of hyperkalaemia or suspected digoxin toxicity (SDT) according to diabetes status (the latter adverse event was defined by and reported by the investigator).

All analyses were undertaken using SAS version 9.3 (SAS Institute, Inc., Cary, NC, USA).

3. RESULTS

Of the 6800 patients with heart failure and reduced ejection fraction (HF-REF) randomised in DIG, 1933 patients (28.4%) were reported by investigators to have diabetes (i.e. medical history of diabetes at baseline).

3.1. Patients with and without diabetes

Patients with diabetes were slightly older, more often women and had more symptoms and signs and worse NYHA functional class than those without diabetes (Table 1). Patients with diabetes also had a higher average BMI, systolic blood pressure, heart rate and creatinine. A history of coronary heart disease and hypertension was more common in individuals with diabetes compared to those without. Diuretics were used more commonly in patients with diabetes compared to those without.

3.2. Daily dose of digoxin

Overall, the daily dose of digoxin taken was 0.125mg in 17.5%, 0.250mg in 70.6%, 0.375mg in 10.3% and 0.500mg in 1.1% of patients (median daily dose 0.250 mg). In patients with diabetes, the daily dose of digoxin taken was 0.125 mg in 17.5%, 0.250 mg in 69.1%, 0.375 mg in 12.7% and 0.500 mg in 0.8%. In patient without diabetes, the daily dose of digoxin taken was 0.125 mg in 20.3%, 0.250 mg in 69.5%, 0.375 mg in 9.0% and 0.500 mg in 1.1%. The median daily dose for patients with diabetes and those without was the same (0.250 mg).

3.3. Clinical outcomes

The major clinical outcomes are shown in Table 2 and Figures 1-4.

3.3.1. Cardiovascular death or heart failure hospitalisation: Overall, 1653 placebo treated patients (rate 20.6 per 100 patient years) and 1501 (rate 17.3) digoxin treated patients experienced the composite outcome of cardiovascular death or heart failure hospitalisation (hazard ratio 0.85, 95% CI 0.79-0.91; p<0.001). The effect of digoxin on this outcome in patients with and without diabetes is shown in Table 2 and Figure 1. Although the relative risk reduction with digoxin in patients with diabetes (10% [95%CI: -20 to +1%]) was numerically smaller than in those without diabetes (17% [-24 to -10%]), the test for interaction was not significant (p=0.27).

3.3.2. Cardiovascular death: Overall, 1004 placebo treated patients (rate 10.1 per 100 patient years) and 1016 (rate 10.3) digoxin treated patients died from a cardiovascular death (HR 1.01, 95%CI: 0.93-1.11; p=0.782). The effect of digoxin on this outcome in patients with and without diabetes is shown in Table 2 and Figure 2. The lack of effect of digoxin on this outcome was similar, irrespective of diabetes status.

3.3.3. Heart failure hospitalisation: Overall, 1180 placebo treated patients (rate 14.7 per 100 patient years) and 910 (rate 10.5) digoxin treated patients were hospitalised at least once for heart failure (HR 0.72, 95%CI: 0.66-0.79; p<0.001). The effect of digoxin on this outcome in patients with and without diabetes is shown in Table 2 and Figure 3. The relative risk reduction with digoxin in patients with diabetes (21%, 9 to 32%) was numerically smaller than in patients without diabetes (31%, 23 to 38%) although the test for interaction was not significant (p=0.14).

Overall, there were 3046 hospital admissions (taking account of patients having more than one admission) in the placebo group and 2340 in the digoxin group (p<0.001). In patients with diabetes these numbers were 1085 and 895, respectively (p=0.033) and in those without diabetes 1961 and 1445, respectively (p<0.001). The incidence rate ratio (for digoxin

compared with placebo) in patients with diabetes was 0.88 (95%CI: 0.69-1.13) and 0.65 (0.53-0.80) in patients without diabetes.

3.3.4. Heart failure death or heart failure hospitalisation: Overall, 1291 placebo treated patients (rate 16.1 per 100 patient years) and 1041 (rate 12.0) digoxin treated patients experienced the composite outcome of heart failure death or heart failure hospitalisation (hazard ratio 0.75, 95% CI 0.69-0.82; p<0.001). The effect of digoxin on this outcome in patients with and without diabetes is shown in Table 2 and Figure 4. Although the relative risk reduction with digoxin in patients with diabetes 20% (95% CI, 8 to 30%) was numerically smaller than in those without diabetes 27% (19 to 34%), the test for interaction was not significant (p=0.30).

3.3.5. All-cause death: Overall, 1194 placebo treated patients (rate 12.1 per 100 patient years) and 1181 (rate 11.9) digoxin treated patients died from all-cause death (HR 0.99, 95% CI 0.91-1.07; p=0.801). The effect of digoxin on this outcome in patients with and without diabetes is shown in Table 2. The lack of effect of digoxin on this outcome was similar, irrespective of diabetes status.

3.4. Serum digoxin concentration, potassium and creatinine

Serum digoxin concentrations were similar in patients with and without diabetes, in keeping with the similar daily dose of digoxin taken in the two groups as reported above (Table 3). Potassium concentrations were similar in patients with and without diabetes and in patients treated with placebo and those treated with digoxin.

Serum creatinine concentrations were higher in patients with diabetes compared to those without diabetes (at both 1 month and 12 months). Serum creatinine concentrations were markedly higher in patients experiencing digoxin toxicity irrespective of diabetes status.

3.5. Hyperkalaemia and suspected digoxin toxicity

The proportion of patients with hyperkalaemia and suspected digoxin toxicity in patients with and without diabetes are shown in Table 4. The incidence of mild hyperkalaemia (serum potassium ≥5.5 mmol/l) was higher in patients with than without diabetes; the rate of more severe hyperkalaemia (serum potassium >6.0mmol/l) was low overall and similar in patients with and without diabetes. Hyperkalaemia appeared to be slightly more common in patients treated with digoxin compared to those treated with placebo.

Suspected digoxin toxicity was more common in digoxin treated than in placebo treated patients. Suspected digoxin toxicity in patients randomised to digoxin was more common among patients with diabetes than without (6.5% versus 5.8%), as was hospitalisation for digoxin toxicity (1.4% versus 0.8%).

4. DISCUSSION

As confirmed in the present report, heart failure patients with diabetes have more co-morbidity, worse functional status and much higher rates of adverse outcomes than patients without diabetes.[1-5]

The main benefit of digoxin was to reduce hospitalisation for heart failure. This effect was numerically but not statistically significantly smaller in patients with diabetes compared to those without. However, as the rate of heart failure hospitalisation was much higher in patients with diabetes, even the possibly smaller relative benefit of digoxin was still substantial. Indeed, the absolute benefit in patients with diabetes (4.5 fewer patients admitted at least once per 100 patient years of treatment) was similar to those without diabetes (4.0 fewer patients per 100 patient years). For the composite of heart failure death or heart failure hospitalisation, these absolute risk reductions were 4.6 and 3.8 per 100 patient years of treatment, respectively. Importantly, digoxin reduced repeat as well as first admissions and this benefit too was observed in patients with diabetes as well as in those without. For every 1000 patients with diabetes treated with digoxin, there were 182 fewer hospital admissions (including repeat admissions) over the average duration of follow-up, compared with placebo. The comparable number for patients without diabetes was 214 admissions. These data suggest that digoxin has the potential to provide substantial, clinically meaningful benefits, in patients with HF-REF and diabetes. Of course, DIG was conducted before the demonstration of the value of mineralocorticoid receptor antagonists (MRAs) and beta-blockers (and devices) in HF-REF and whether the same incremental benefits can be obtained in patients taking these two treatments as well as an ACE inhibitor is unknown.

The other important consideration is the tolerability of digoxin in patients with diabetes. Patients with diabetes are more likely to have renal dysfunction, as demonstrated in the present analysis. Reduced renal clearance increases the risk of digoxin toxicity. Despite this, and the relatively high dose of digoxin used in DIG, the risk of digoxin toxicity was low although patients who experienced digoxin toxicity had a higher average serum creatinine at that time (compared with other patients) and suspected digoxin toxicity was more slightly common in patients with diabetes than without.

Although the DIG trial was conducted more than 20 years ago, it remains the only large, prospective, randomized, placebo-controlled outcome trial with digoxin in patients with heart HF-REF. As such, it continues to inform all major international heart failure guidelines. Consequently, it remains the most robust source of information on the effects of digoxin in HF-REF patients with and without diabetes. Given that HF-REF patients with diabetes have generally more severe symptoms than patients without diabetes, they will also have a more frequent indication for digoxin according to current guidelines (where digoxin is particularly indicated in patients with persisting or more severe symptoms despite other recommended therapy). As a result, we believe that our findings still have contemporary relevance. Indeed, a recent systematic review of 52 clinical trials and observational studies demonstrated that individuals treated with digoxin were more likely to have diabetes than those not treated with digoxin and confirmed in a much larger population the lack of mortality risk with digoxin observed in the DIG trial.[14]

In another analysis of the DIG trial, including the 988 patients in the ancillary study with a LVEF >45%, cluster analysis suggested that digoxin treatment may be associated with a higher mortality in patients with a heart failure with preserved ejection fraction (HF-PEF) phenotype (including older age higher LVEF and systolic blood pressure, female sex and

history of diabetes).[15] Consequently, we do not know whether our findings with respect to the safety of digoxin in patients with HF-REF also apply to patients with HF-PEF.

This report has a number of limitations. This is a retrospective analysis. DIG was conducted before the demonstration of benefit of several different drugs (including beta-blockers and MRAs) and devices. As with all trials, the patients enrolled were selected according to inclusion and exclusion criteria (as detailed in the Methods section). Suspected digoxin toxicity was investigator reported and not adjudicated or always confirmed by serum measurements. Thus, serum concentrations of digoxin, potassium and creatinine are available only for a part of the study cohort. Heart rate was not measured during follow-up.

In summary, when added to an ACE inhibitor digoxin reduces heart failure hospitalisation in HF-REF patients with and without diabetes without any major off-setting toxicity. Although the *relative* risk reduction in patients with diabetes may be somewhat smaller than in individuals without diabetes, the absolute risk reduction remains substantial (because the absolute rate of adverse outcomes is much higher in patients with diabetes).

APPENDIX: *VICCTA-Heart Failure Steering Committee members: K.R Lees, John J.V McMurray and A.H Abdul-Rahim.

ACKNOWLEDGEMENTS: We thank all those involved in the DIG trial. The DIG trial data were obtained from The Virtual International Cardiovascular and Cognitive Trials Archive (VICCTA), [URL: www.viccta.org], a not-for-profit collaboration of researchers from academia and commercial organisations. The VICCTA Steering Committee members have each contributed to the organisation of contributing trials, and where these have involved industry support, they have acknowledged that within the original publications. Some data within VICCTA were obtained from the National Heart Lung Blood Institutes (NHLBI) Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC) and any analysis of these data does not necessarily reflect the opinions or views of NHLBI.

CONFLICT OF INTEREST: The authors report no relationships that could be construed as a conflict of interest.

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FIGURES LEGENDS

Figure 1: Kaplan Meier cumulative risk of the composite outcome of CV death or HF hospitalisation in patients with and without diabetes.

Figure 2: Kaplan Meier cumulative risk of CV death in patients with and without diabetes.

Figure 3: Kaplan Meier cumulative risk of HF hospitalisation in patients with and without diabetes.

Figure 4: Kaplan Meier cumulative risk of the composite outcome of HF death or HF hospitalisation in patients with and without diabetes.

TABLES

Table 1. Baseline characteristics according to diabetes status at baseline.

	All patients (N= 6800)	**Without Diabetes** (n= 4867)	**With Diabetes** (n= 1933)
Demographics, **n (%)**			
Age, year	63.5 ± 10.9	63.2 ± 11.5*	64.2 ± 9.3*
Caucasians	5809 (85.4)	4218 (86.7)*	1591 (82.3)*
Female sex	1519 (22.3)	1008 (20.7)*	511 (26.4)*
NYHA class			
I	907 (13.3)	699 (14.4)*	208 (10.8)*
II	3664 (53.9)	2689 (55.3)*	975 (50.4)*
III	2081 (30.6)	1392 (28.6)*	689 (35.6)*
IV	142 (2.1)	83 (1.7)*	59 (3.1)*
Duration of heart failure, year	2.5 ± 3.1	2.5 ± 3.1	2.5 ± 3.1
LV Ejection Fraction, %	28.5 ± 8.9	28.3 ± 9.0*	29.1 ± 8.6*
Cardiothoracic ratio	0.53 ± 0.1	0.53 ± 0.1*	0.54 ± 0.1*
No. of signs or symptoms of CHF[†]			
0	73 (1.1)	60 (1.2)*	13 (0.7)*
1	149 (2.2)	117 (2.4)*	32 (1.7)*
2	483 (7.1)	389 (8.0)*	94 (4.9)*
3	607 (8.9)	465 (9.6)*	142 (7.4)*
≥4	5486 (80.7)	3834 (78.8)*	1652 (85.5)*
Baseline vital signs			
BMI, kg/m^2	27.1 ± 5.2	26.5 ± 5.0*	28.6 ± 5.5*
BP, mmHg			
Systolic	125.8 ± 19.9	124.6 ± 19.7*	128.8 ± 20.3*
Diastolic	74.9 ± 11.3	75.0 ± 11.3*	74.8 ± 11.2*
Heart rate, beats/min	78.8 ± 12.7	77.8 ± 16.9*	81.2 ± 12.3*

	All patients (N= 6800)	Without Diabetes (n= 4867)	With Diabetes (n= 1933)
Laboratory measurements			
Potassium, mmol/L, *median (IQR)*	4.3 (4.1-4.6)	4.3 (4.0-4.6)*	4.4 (4.1-4.7)*
Serum creatinine, µmol/L	113.4 ± 32.6	112.0 ± 30.9*	117.1 ± 36.2*
Medical history, **n (%)**			
Myocardial Infarction	4419 (65.0)	3126 (64.2)*	1293 (66.9)*
Angina	1821 (26.8)	1248 (25.6)*	573 (29.6)*
Hypertension	3084 (45.4)	1971 (40.5)*	1113 (57.6)*
Previous digoxin use	3017 (44.4)	2149 (44.2)	868 (44.9)
Medication, **n (%)**			
Potassium-sparing diuretic	517 (7.6)	367 (7.5)	150 (7.8)
Other diuretics	5325 (78.3)	3688 (75.8)*	1637 (84.7)*
ACE inhibitor	6422 (94.4)	4587 (94.3)	1835 (94.9)
Nitrate	2898 (42.6)	1896 (39.0)*	1002 (51.8)*
Hydralazine	141 (2.1)	74 (1.5)*	67 (3.4)*
Randomised to digoxin	3397 (50.0)	2436 (50.1)	961 (49.7)

All continous values are given in mean ± standard deviation unless stated otherwise. CHF: chronic heart failure; n(%): number of observations (percentage of observations within the group); NYHA: New York Heart Association; BMI: body mass index; ACE: angiotensin converting enzyme; LV: left ventricle; IQR: interquartile range; DIG: Digitialis Investigation Group.

† The clinical signs or symptoms studied included rales, elevated jugular venous pressure, peripheral oedema, dyspnoea at rest or on exertion, orthopnoea, limitation of activity, S_3 gallop and radiological evidence of pulmonary congestion.

* Significant difference, $p<0.05$.

Table 2. Clinical outcomes according to diabetes status and randomised treatment assignment.

	No diabetes			Diabetes			
	Placebo (n=2431)	**Digoxin** (n=2436)	**HR** (95% CI)	**Placebo** (n=972)	**Digoxin** (n=961)	**HR** (95% CI)	**p-value for interaction**
CV death or HF hospitalisation, n (rate*)	1086 (18.2)	966 (14.9)	0.83 (0.76,0.90)	567 (27.6)	535 (24.6)	0.90 (0.80,1.01)	0.27
CV death, n (rate)	664 (9.2)	665 (9.2)	0.99 (0.89,1.11)	340 (12.6)	351 (13.3)	1.06 (0.92,1.24)	0.47
HF hospitalisation, n (rate)	760 (12.7)	563 (8.7)	0.69 (0.62,0.77)	420 (20.5)	347 (16.0)	0.79 (0.68,0.91)	0.14
HF death or HF hospitalisation, n (rate)	831 (13.9)	654 (10.1)	0.73 (0.66,0.81)	460 (22.4)	387 (17.8)	0.80 (0.70,0.92)	0.30
HF death, n (rate)	288 (4.0)	256 (3.5)	0.88 (0.75,1.04)	161 (5.9)	138 (5.2)	0.89 (0.71,1.12)	0.98
All-cause death, n (rate)	790 (11.0)	772 (9.9)	0.97 (088,1.07)	460 (14.9)	387 (15.5)	1.04 (0.91,1.20)	0.40

* per 100 patient-years. CV = cardiovascular. HF = heart failure

Table 3. Serum concentrations of digoxin, potassium and creatinine.

Blood parameters	Timeline	Without diabetes		With diabetes	
		Placebo	Digoxin	Placebo	Digoxin
Serum digoxin[*] (ng/mL)	1M[† ‡]		0.8 ± 0.5		0.9 ± 0.5
	12M[† ‖]		0.8 ± 0.5		0.8 ± 0.5
	SDT[a]		1.1 ± 0.9		1.2 ± 0.8
Potassium (mmol/L)	1M[§]	4.4 ± 0.5	4.4 ± 0.5	4.5 ± 0.5	4.5 ± 0.5
	12M[#]	4.4 ± 0.5	4.4 ± 0.5	4.4 ± 0.5	4.5 ± 0.4
	SDT[b]	4.2 ± 0.4	4.4 ± 0.6	4.5 ± 0.7	4.5 ± 0.8
Serum creatinine (umol/L)	1M[ɖ]	115.3 ± 37.5	109.9 ± 33.7	119.7 ± 38.8	115.1 ± 36.5
	12M[**]	115.9 ± 37.7	113.5 ± 33.6	129.1 ± 58.4	120.4 ± 48.8
	SDT[c]	113.9 ± 35.8	137.5 ± 51.9	162.9 ± 44.5	172.8 ± 91.8

1M indicates 1-month visit; 12M: 12-month visit; SDT: suspected digoxin toxicity. Values are given in mean ± standard deviation.

[*] Digoxin concentration for patients who received digoxin or patient with suspected digoxin toxicity during the trial.

[†] Blood samples obtained 6 hours after the last dose.

[‡] Data available for 1497 patients (1084 without diabetes and 413 with diabetes).

[§] Data available for 1608 patients (1140 without diabetes and 468 with diabetes).

[‖] Data available for 1294 patients (957 without diabetes and 337 with diabetes).

[#] Data available for 1036 patients (770 without diabetes and 266 with diabetes).

[ɖ] Data available for 1616 patients (1144 without diabetes and 472 with diabetes).

[**] Data available for 1036 patients (770 without diabetes and 266 with diabetes).

[a] Data available for 222 patients (156 without diabetes and 66 with diabetes).

[b] Data 102 patients (77 without diabetes and 25 with diabetes).

[c] Data 104 patients (79 without diabetes and 25 with diabetes).

Table 4. Proportions of patients with hyperkalaemia or suspected digoxin toxicity (SDT) according to diabetes status.

Events	**Timeline**	**Without diabetes**, n(%)		**With diabetes**, n(%)	
		Placebo	**Digoxin**	**Placebo**	**Digoxin**
Hyperkalaemia, $K^+ \geq 5.5$mmol/L	1M[*]	8 (0.7)	11 (1.0)	11 (2.3)	8 (1.7)
	12M[†]	5 (0.6)	9 (1.2)	3 (1.1)	4 (1.5)
	SDT[‡]	0 (0.0)	1 (1.3)	2 (8.0)	2 (8.0)
Hyperkalaemia, $K^+ > 6.0$mmol/L	1M[*]	2 (0.2)	7 (0.6)	1 (0.2)	3 (0.6)
	12M[†]	2 (0.3)	4 (0.5)	0 (0.0)	2 (0.8)
	SDT[‡]	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)
SDT[§]		191 (3.9)	280 (5.8)	79 (4.1)	126 (6.5)
Hospitalisation due to SDT		20 (0.4)	40 (0.8)	11 (0.6)	27 (1.4)

1M indicates 1-month visit; 12M: 12-month visit; SDT: suspected digoxin toxicity. Values are given in 'number (percentage)' format.

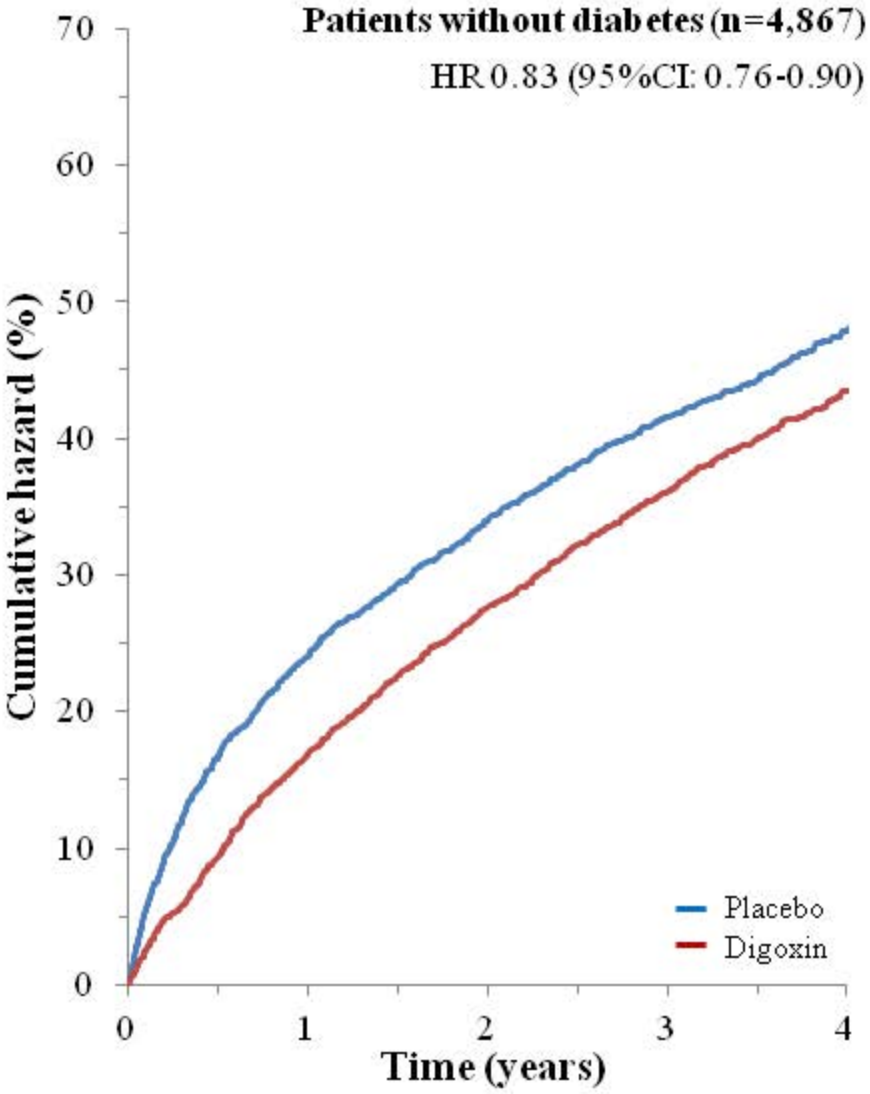
[*] Data available for 1608 patients (1140 without diabetes and 468 with diabetes).

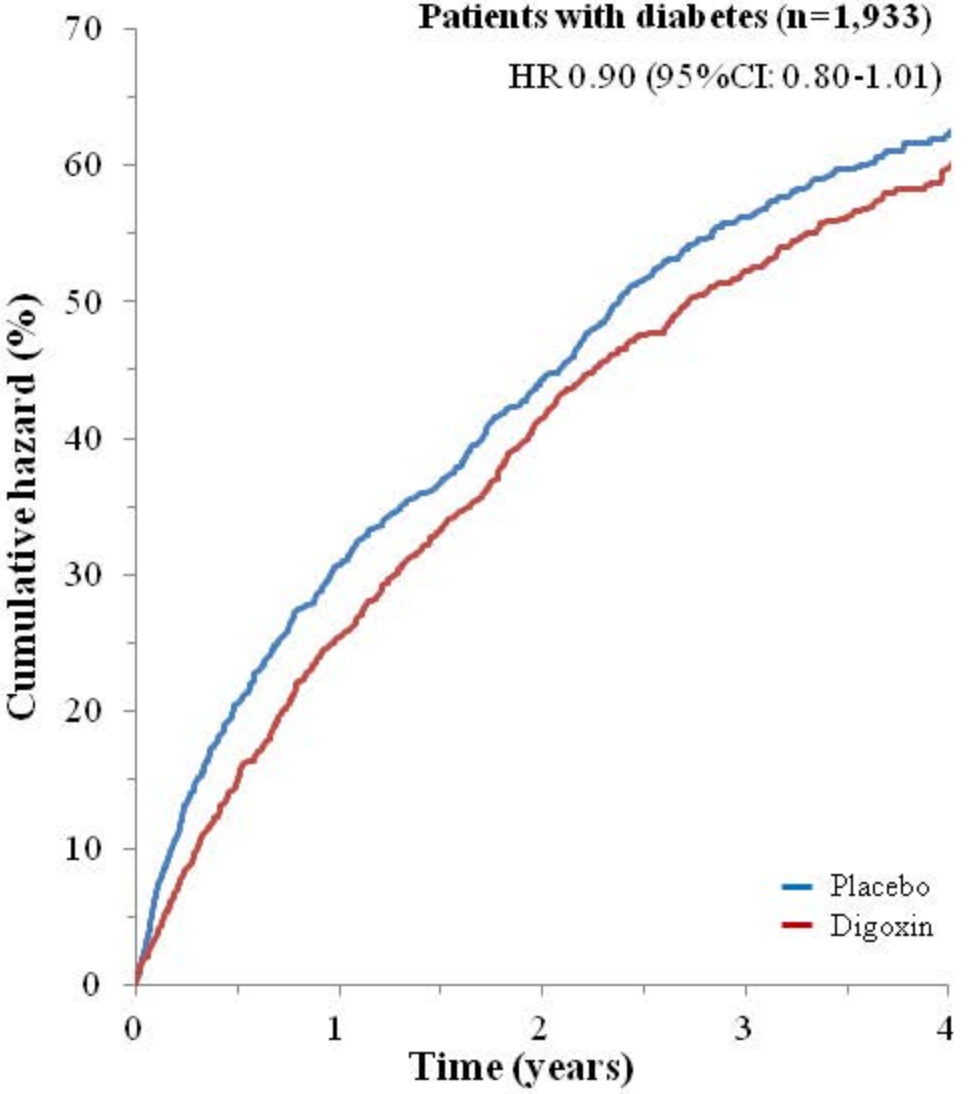
[†] Data available for 1036 patients (770 without diabetes and 266 with diabetes).

[‡] Data available for 102 patients (77 without diabetes and 25 with diabetes).

[§] Data available for 6800 patients (4867 without diabetes and 1933 with diabetes).

FIGURES

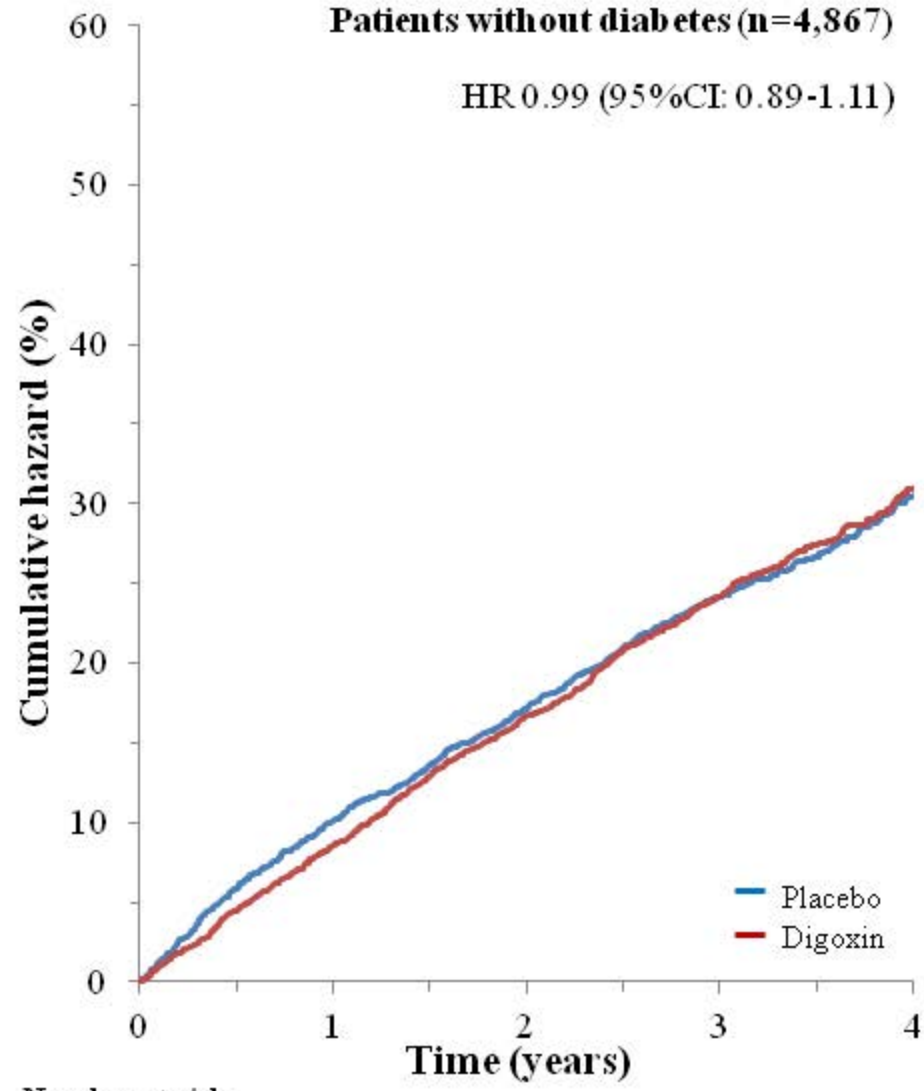


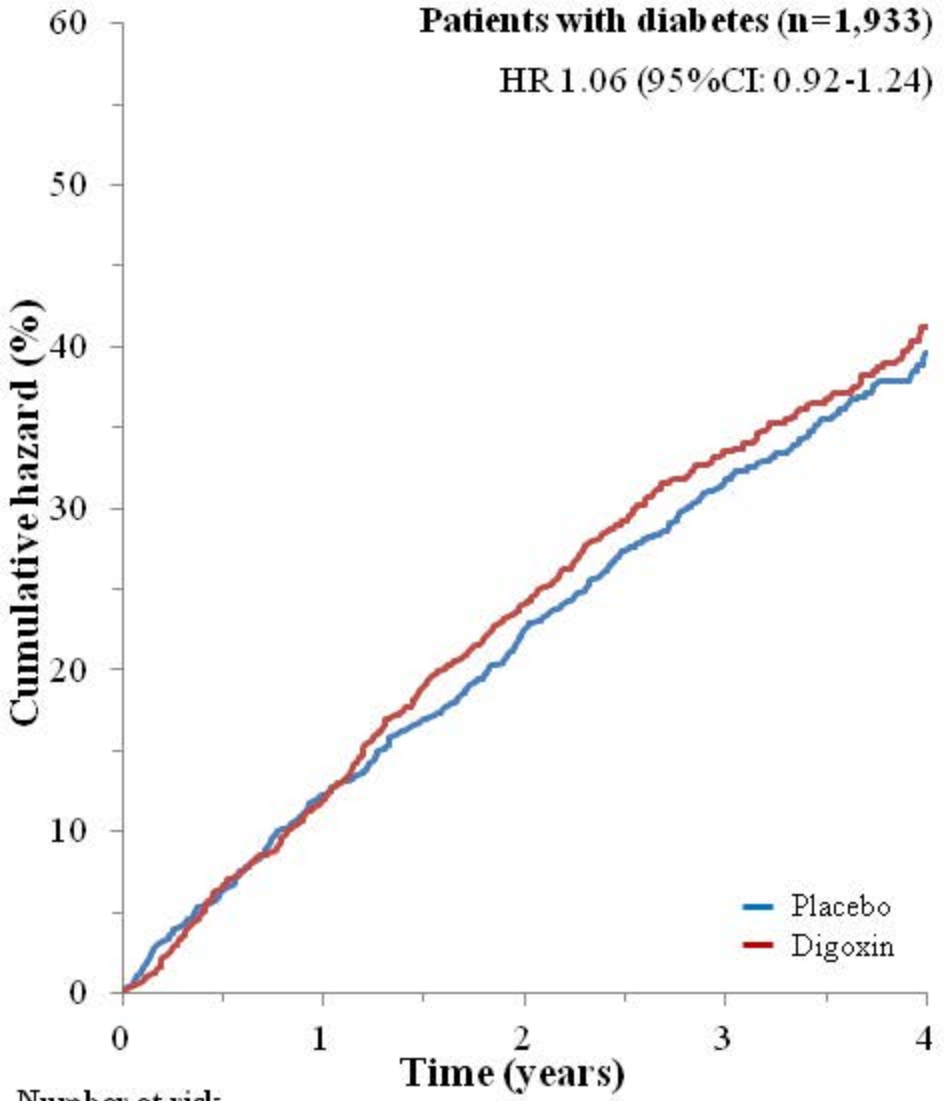


Number at risk					
Placebo	2431	1811	1553	1075	432
Digoxin	2436	1993	1702	1182	433

Number at risk					
Placebo	972	662	518	322	114
Digoxin	961	703	539	339	145

Interaction, p=0.271

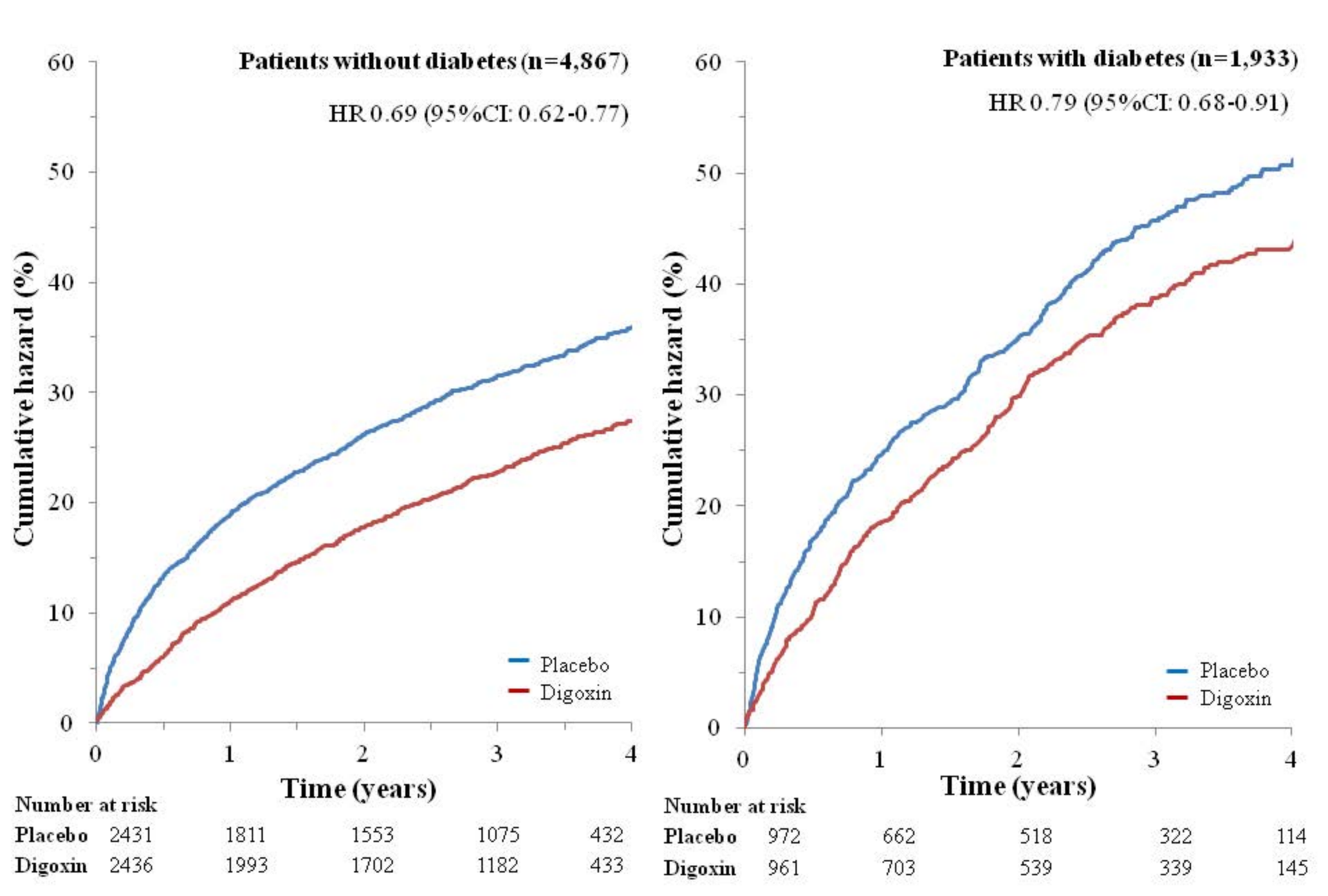


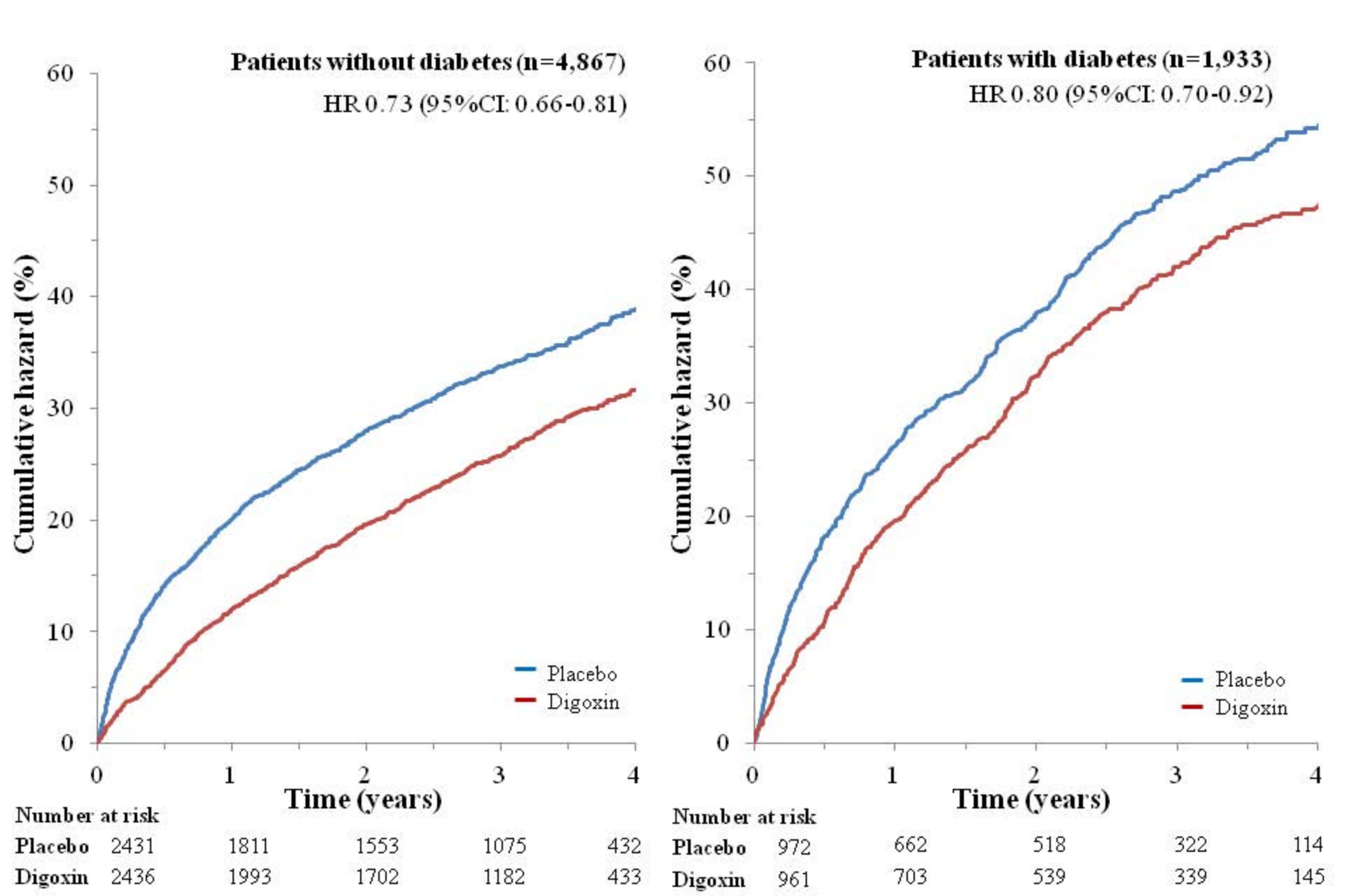


Number at risk					
Placebo	2431	2139	1936	1382	563
Digoxin	2436	2192	1954	1384	540

Number at risk					
Placebo	972	837	716	499	171
Digoxin	961	827	690	456	197

Interaction, p=0.471


Patients without diabetes (n=4,867)
HR 0.69 (95%CI: 0.62-0.77)
Cumulative hazard (%)
Time (years)
Placebo
Digoxin
Number at risk
Placebo 2431 1811 1553 1075 432
Digoxin 2436 1993 1702 1182 433
Patients with diabetes (n=1,933)
HR 0.79 (95%CI: 0.68-0.91)
Cumulative hazard (%)
Time (years)
Placebo
Digoxin
Number at risk
Placebo 972 662 518 322 114
Digoxin 961 703 539 339 145
Interaction, p=0.140



Interaction, p=0.303