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DIGOXIN IN PATIENTS WITH ADVANCED HEART FAILURE AND SINUS RHYTHM – IS THERE ANY BENEFIT?

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Abstract

Background

Digoxin is one of the oldest drugs used in heart failure (HF) treatment. It may be considered in patients in sinus rhythm with heart failure with reduced ejection fraction (HFrEF). However, digoxin use in this context remains a matter of controversy as recent studies have shown an increased risk of mortality and malign arrhythmias in patients taking this drug.

The purpose of this study is to assess the prognostic impact of digoxin in patients in sinus rhythm submitted to cardiac resynchronization therapy (CRT).

Methods

A retrospective study including 297 consecutive patients with advanced HF, in sinus rhythm, submitted to CRT between February 2004 and January 2016, in a single centre.

Patients were divided in two groups regarding digoxin use (with digoxin - DG and without digoxin - NDG). A mean follow-up of 4.85 ± 3.37 years was performed. Multivariate Cox regression was used to evaluate the association between digoxin use and outcomes. The primary endpoint was the combination of cardiovascular (CV) hospitalization, heart transplantation or all-cause mortality.

Results

The mean age was 64±11 years, with 67% of the cohort being male. Digoxin was prescribed in 104 (35%) patients. These patients were younger (60±11 in DG vs 66±10 in NDG, $p < 0.001$). The two groups did not differ significantly regarding HF functional class (78.2% patients in New York Heart Association class III or IV in NDG vs 82.7% in the DG, p=0.362), HF aetiology (35.2% ischemic patients in NDG vs 28.8% in DG, $p = 0.264$), QRS duration (145.3 ms ± 26. 3 ms in NDG vs 143.8 ms ± 27.4 ms in DG, $p = 0.711$) and baseline left ventricular ejection fraction (LVEF) (26% ± 6.5% in NDG vs 25.6% ± 7.31% in DG, $p = 0.094$). The proportion of responders to CRT was similar between groups (55.9% responders in NDG vs 53.7% in DG, $p = 0.78$). Digoxin group presented a significantly higher mortality rate (42.3% in DG vs 25.4% in NDG, $p = 0.003$), and a higher hospitalization rate due to HF (53% in DG vs 35.8% in NDG, $p = 0.011$). There was no association between digoxin use and the occurrence of ventricular tachycardia (31.7% in DG vs 40.1% in NDG, $p = 0.155$).

After adjusting for potential confounders in the Cox regression model, digoxin use was identified as an independent predictor of all-cause mortality (HR= 1.97, CI 95 [1.09 – 3.57], p=0.024), and of hospitalization due to HF (HR=2.83, CI 95 [1.40 – 5.70], $p = 0.004$).

Conclusions

The use of digoxin in patients in sinus rhythm with HFrEF proved to be an independent predictor of all-cause mortality, and hospitalizations due HF. This data suggests that digoxin should be avoided in patients in sinus rhythm, with advanced systolic HF, who have criteria for CRT. However, further investigation is warranted to verify if digoxin has a direct negative influence in the natural history of HFrEF or if it is only a marker of disease severity and worse prognosis.

Key words: digoxin, heart failure, sinus rhythm, cardiac resynchronization therapy.

Resumo

Objetivos

A digoxina é um dos fármacos mais antigos usados no tratamento da insuficiência cardíaca (IC). O seu uso pode ser considerado em doentes em ritmo sinusal com insuficiência cardíaca e fração de ejeção reduzida (ICFEr). Contudo, tem surgido alguma controvérsia relativamente ao uso da digoxina neste contexto após estudos recentes terem sugerido um aumento do risco de mortalidade e arritmias malignas.

O objetivo deste estudo consiste na avaliação do impacto prognóstico da digoxina em doentes em ritmo sinusal submetidos a terapêutica de ressincronização cardíaca (TRC).

Métodos e população

Estudo retrospetivo que incluiu 297 doentes com IC avançada e ritmo sinusal, submetidos a TRC entre fevereiro de 2004 e janeiro de 2016, num único centro.

Os doentes foram divididos em dois grupos, de acordo com o tratamento com digoxina (com digoxina – DG - e sem digoxina - NDG). Foi realizado um seguimento clínico de 4,85 ± 3,37 meses, em média. A regressão de Cox foi utilizada para identificar preditores independentes de *outcomes*. O *endpoint* primário foi um *endpoint* combinado de internamento de causa cardiovascular (CV), transplante cardíaco ou mortalidade de todas as causas.

Resultados

A média da idade de 64 ± 11 anos, sendo 67% da *coorte* do sexo masculino. A digoxina foi prescrita a 104 doentes (35%). Estes doentes eram mais jovens (60±11 DG vs 66±10 NDG, $p < 0,001$). Os dois grupos não diferiam significativamente em relação à classe funcional IC (78,2% dos doentes em classe funcional III ou IV da New York Heart Association no NDG vs 82,7% no DG, $p = 0,362$), em relação à causa da IC (35,2% causa isquémica no NDG vs 28,8% DG, $p = 0,264$), duração do QRS (145,3 ± 26,3 NDG vs 143,8 ± 27,4 DG, $p = 0,711$) e fração de ejeção do ventrículo esquerdo (FEVE) na linha de base (26 ± 6,5 NDG vs 25,6 ± 7,31 DG, $p = 0,094$). A proporção de respondedores à TRC foi semelhante entre os dois grupos (55,9% NDG vs 53,7% DG, $p = 0,78$). O grupo da digoxina apresentou uma taxa de mortalidade significativamente maior (42,3% DG vs 25,4% NDG, $p = 0,003$), e uma taxa de hospitalização por IC superior (53% in DG vs 35,8% in NDG, $p = 0,011$). Não foram identificadas quaisquer associações entre o uso de digoxina e a ocorrência de taquiarritmias ventriculares (31,7% DG vs 40,1% NDG, $p = 0,155$).

Na regressão de Cox, tendo em conta potenciais fatores confundentes, a digoxina foi um preditor independente de mortalidade de todas a causas (HR= 1.97, CI 95 [1.09 – 3.57], *p* = 0.024), e de hospitalização por IC (HR=2.83, CI 95 [1.40 – 5.70], *p* = 0.004).

Conclusões

O uso da digoxina em doentes com ICEFr em ritmo sinusal, parece ser um preditor independente de todas as causa de mortalidade e de hospitalização por IC. Os resultados sugerem que a digoxina deve ser evitada em doentes em ritmo sinusal, com IC sistólica avançada, com critérios para TRC. Ainda assim, mais estudos devem ser realizados no sentido de verificar se a digoxina tem um impacto negativo direto na história natural da ICFEr ou se é apenas um marcador de doença avançada e de pior prognóstico.

Palavras-chave: Digoxina, insuficiência cardíaca, ritmo sinusal, terapia de ressincronização cardíaca.

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List of abbreviations

ACE-I – Angiotensin Converter Enzyme Inhibitor
AF- Atrial Fibrillation
Af- Atrial flutter
ARBs – Angiotensin II receptor blocker
BB- Beta-blockers
BNP – Brain Natriuretic Peptide
CHF- Congestive Heart Failure
CRT – Cardiac Resynchronization Therapy
CRT – D - Cardiac Resynchronization Therapy with Defibrillator
CRT – P- Cardiac Resynchronization Therapy with Pacemaker
CV – cardiovascular
DG – Digoxin Group
ESC- European Society of Cardiology
HF- Heart Failure
HFrEF – Heart Failure with reduced Ejection Fraction
ICD – Implantable Cardioverter Defibrillator
LV – Left Ventricle
LVEF – Left Ventricular Ejection Fraction
LVESV – Left ventricular End-Systolic Volume
LVEDV - Left ventricular End-Diastolic Volume
NGD –Non-Digoxin Group
NYHA – New York Heart Association
VF – Ventricular Fibrillation
VT – ventricular Tachyarrhythmias

1 Introduction

Heart failure (HF) is a serious public health problem, affecting 1–2% of the adult population in developed countries, rising to ≥10% among people older than 70 years of age[1]. Despite the significant advances in therapies and prevention, mortality and morbidity are still high and quality of life poor [2].

During the last two decades, digoxin has been considered in the therapeutic armamentarium of HF with reduced ejection fraction (HFrEF)[3]. The Digitalis Investigator Group (DIG), a large randomized, placebo-controlled trial in patients with HF, showed that digoxin significantly reduced hospitalizations for HF with no impact on all-cause or cardiovascular mortality. However, observational studies and post hoc analysis of other subgroups of the DIG trial have reported adverse effects of digoxin on mortality in patients with atrial fibrillation (AF) and those with HF. Consequently, the use of digoxin has progressively declined in last years[4, 5]. Currently, the European Society of Cardiology (ESC) gives class IIb recommendation for use of digoxin in HFrEF to decrease HF hospitalizations [1].

Cardiac resynchronization therapy (CRT) is a well-established treatment for symptomatic patients with HFrEF who remain in New York Heart Association (NYHA) functional classes II to IV, despite optimal medical therapy with a wide QRS complex and reduced left ventricular ejection fraction (LVEF) (<35%)[4].

Results from several studies including randomized controlled trials and observational studies have consistently demonstrated significant reduction in the combined endpoint of all-cause mortality and all-cause hospitalization and significant improvement in quality of life, functional status, and exercise capacity in patients who are assigned to active CRT [6, 7].

Some studies have tried to assess the effect of digoxin in patients submitted to CRT [5, 8-10]. However, the effect of adding digoxin in patients submitted to CRT has not been completely clarified yet.

The current study aimed to investigate the effects of digoxin in HF patients submitted to CRT on all-cause mortality, hospitalizations due to acute HF and ventricular tachyarrhythmias.

2 Population and methods

2.1 Study population

We analyzed all consecutive patients who underwent CRT implantation between February 2004 to January 2016 from a prospectively maintained database.

Inclusion criteria included the following baseline criteria: (1) left ventricular ejection fraction (LVEF) ≤ 35%, (2) NYHA class II to IV, (3) native QRS duration ≥120ms, sinus rhythm and optimal medical treatment.

CRT devices were implanted by electrophysiologists using standard transvenous techniques. Left ventricular leads were inserted into a venous branch of the coronary sinus, with specific locations chosen for stability, acceptable capture thresholds, lack of phrenic nerve stimulation, and anatomic suitability.

After CRT, patients were evaluated every 6 months or before if clinical situation justified. The protocol was approved by our institutional Research Ethics Committee. All patients gave informed consent, and the study complied with the Declaration of Helsinki.

2.2 Echocardiographic evaluation

Standard echocardiography was performed before and 6 months after CRT. The following measurements were taken: left atrial (LA) volume, left ventricular (LV) diameters and volume, LVEF using Simpson method, and evaluation of mitral regurgitation.

2.3 Endpoints and Long-term Follow-up

We defined as primary endopoint the combination of CV hospitalizations, heart transplant or all-cause mortality. Secondary endopoints included the individual components of the primary endpoint and appropriated device therapies due to ventricular arrhythmias.

A mean follow-up 4.85 ± 3.37 years was performed. Information about outcomes was obtained from outpatient clinic records, emergency department admissions records and device monitoring consultation. We defined as ventricular arrhythmia ventricular tachycardia episodes detected by CRT lasting more than 30 seconds or that required antitachycardia pacing or appropriate shock (for CRT with backup defibrillator). All electrograms were analyzed by an electrophysiologist at the time of presentation and reviewed during data acquisition. Device reprogramming, medication changes, ablation procedures, and/or hospital admission were at left discretion of the treating physician(s).

2.4 Statistical analysis

Statistical analyses were performed using SPSS software version 24 (IBM Corp., Armonk, NY, USA). To test the normality of the variables, the Kolmogorov-Smirnov statistic was used. Baseline characteristics were presented as mean (standard deviation) or median (interquartile range) in the case of non-normal distribution. Qualitative variables are expressed as absolute frequencies and percentage. Chi-square and t-student tests for categorical and continuous variables, respectively, were used to compare the study groups. Cox proportional hazards regression, accounting for the potential confounders, was used to evaluate the impact of digoxin on time-dependent clinical outcomes.

A two-tailed *p* value <0.05 was considered statistically significant with a confidence interval of 95%.

3 Results

3.1 Patients characteristics

The baseline characteristics of the 297 patients included in the study are shown in Table 1. At the time of CRT implantation, 104 (35%) patients were taking digoxin (DG) and 193 (65%) were not (NDG).

The mean age of study population was 64.0 ± 11 years and 66.7% were male. Before resynchronization therapy, the mean QRS duration was 144.70 ± 26.67 ms, mean LVEF was 25.47 ± 6.83 %. Most patients were under modifying prognosis therapeutic drugs at CRT implantation time (Figure 1). The majority of patients presented a non-ischaemic aetiology of the HF (67.0%) and were in advanced NYHA class (8.4% in class IV, 57.6% in class III and 19.9% in class II). The great majority of patients (80.1%) received a CRT with a backup defibrillator (CRT-D).

Table 1 Baseline characteristics of study population

Male Gender (%)	66.7 (n = 198)
Age (years)*	63.73 ± 11.07
QRS (ms) *	144.70 ± 26.67
HR (beats/min) *	68.43 ± 13.74
LVEF (%)*	25.47 ± 6.83

CRT-D/P = Cardiac Resynchronisation Therapy –Defibrillator / Pacemaker; HF = Heart Failure; HR = Heart Rate; LVEF = Left Ventricular Ejection Fraction; NYHA = New York Heart Association.

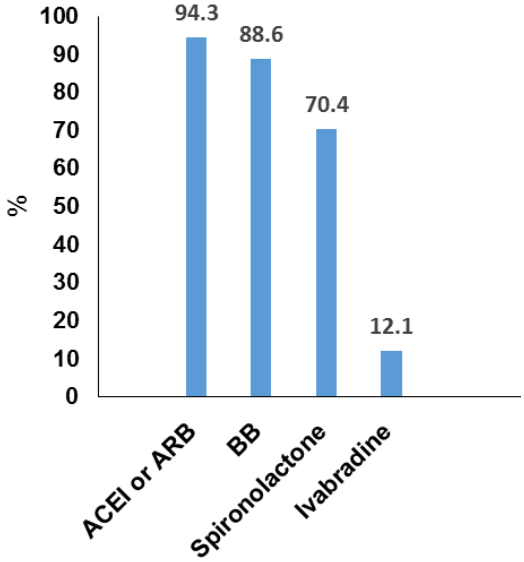

Figure 1 Modifying prognosis therapeutic drugs at CRT implantation time

ACEI = Angiotensin Converter Enzyme Inhibitor; ARB = Angiotensin II Receptor Blocker; BB= Beta – blocker.

The comparison between both groups is represented in Tables 2 and 3. Patients receiving digoxin were on average 6 years younger (59.77 ± 11.85 vs 65.89 ± 10.17, $p < 0.001$). Groups did not differ significantly regarding CV risk factors prevalence, QRS duration or HF aetiology. However, regarding baseline treatment, NDG had more prescriptions with spironolactone ($p < 0.001$).

Table 2 Comparison of baseline characteristics between DG and GND

	NDG (n=193)	**DG (n=104)**	***p* value**
Age (years)*	65.89 ± 10.17	59.77 ± 11.85	<0.001
Male gender (%)	64.8 (n = 125)	70.2 (n = 73)	0.344
Ischaemic aetiology (%)	35.2 (n = 68)	28.8 (n= 30)	0.264
NYHA class III or IV (%)	78.2 (n = 151)	82.7% (n = 86)	0.362
HR (beats/min) *	67.16 ± 13.19	70.23 ±14.39	0.169
QRS (ms)*	145.28 ± 26.27	143.79 ± 27.44	0.711
CRT-D / CRT-P (%)	79.8/ 20.2	80.8/ 19.2	0.841
Diabetes (%)	31.9 (n = 60)	29.6 (n = 29)	0.687
Hypertension (%)	63.6 (n = 98)	50.0 (n = 30)	0.068
Hyperlipidemia (%)	74.7 (n = 118)	63.5 (n = 40)	0.096
CKD	28.3	27.5	0.906
BB (%)	89.6 (n = 173)	86.5 (n =90)	0.424
ACE- I (%)	95.3 (n = 184)	92.3 (n = 96)	0.284
Spironolactone (%)	61.1(n =118)	87.5 (n = 91)	<0.001

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*Mean ± standard deviation.

ACEI = Angiotensin Converter Enzyme Inhibitor; BB= Beta – blocker CRT-D/P = Cardiac Resynchronization Therapy Defibrillator/ Pacemaker; CKD = Chronic Renal Disease; NYHA = New York Heart Association.

The comparison of echocardiographic parameters, BNP (Brain peptide natriuretic) levels and response to CRT between groups is presented in Table 3. The two groups did not differ regarding LV and LA volumes, LVEF and BNP levels.

The rate of responders to CRT in the study population was 55% and very similar between the two study groups *(*55.9% in NDG and 53.7% DG, *p* = 0.78*).*

However, after CRT cardiac geometry tended to be worse in DG, with a LVEDV significantly larger in DG (237.52 ± 110.50 mL vs 199.61 ±85.99, *p* = 0.023).

At baseline, BNP levels tended to be higher in the DG and after CRT the difference between groups increased (569.88 ± 836.76 pg/ mL versus 331.21 ± 508.88 pg/ mL in NDG, *p* = 0.077).

At baseline, a higher proportion of patients in DG group was in NYHA class III or IV by comparison with the NDG (80.4% vs 74.4%, *p*= 0.0013). As expected, after CRT both groups improved the functional class, however a significantly higher proportion of patients in DG remained in class III or IV at 6 months follow-up by comparison with NDG (42.4% in DG vs 25.2% in NDG, *p*=0.0016).

Table 3 Comparison of echocardiographic parameters, BNP levels and NYHA class before and after CRT between patients with and without digoxin

Parameters	**Before CRT**			**After CRT**		
	NDG	**DG**	***p* value**	**NDG**	**DG**	***p* value**
LA dimensions (mm)*	44.20 ± 7.14	45.43 ± 8.08	0.394	43.56 ± 7.63	45.98 ± 9.05	0.103
LA volume (mL)*	83.22 ± 32.81	97.72 ± 35.09	0.150	74.07 ± 31.79	106.13 ± 47.76	0.067
LVTSV (mL)*	175,09± 70,07	198,17 ± 82,79	0,041	136,77 ± 73,96	69,65 ± 98,69	0,026
LVTDV (mL)*	230.47 ± 84.87	250.68 ± 96.94	0.119	199.61 ± 85.99	237.52 ± 110.50	0.023
LVEF (mL)*	25.99 ± 6.50	24.57 ± 7.31	0.094	35.31 ± 11.38	32.90 ± 12.06	0.145
BNP (pg/ mL) *	230.47 ± 84.87	444.38 ± 660.96	0.083	331.21 ± 508.88	569.88 ± 836.76	0.077
Reponders (%)	--------	-------	------	55.9	53.7	0.777
NYHA class (%) **I** **II** **III** **IV**	 0.6 (n = 1) 26.5 (n = 41) 68.9 (n = 113) 5.5 (n = 9)	 0.0 (n = 0) 19.6 (n = 18) 63.0 (n = 58) 17.4 (n =16)	0.013	 26.1 (n = 31) 48.7 (n = 58) 24.4 (n = 29) 0.8 (n = 1)	 17.8 (n =13) 39.7 (n = 29) 34.2 (n = 25) 8.2 (n = 6)	0.016

*mean ± standard deviation.

BNP = Brain Natriuretic Peptide; LVEDV = left ventricular end diastolic volume; LVEF = Left ventricular ejection fraction; LVESV= Left Ventricular End-Systolic Volume; NYHA = New York Heart Association class.

3.1 Appropriated device shocks and ventricular arrythmias

Appropriate ICD shocks occurred in 8.7% of patients receiving digoxin and in 7.8% of patients not receiving digoxin at baseline (p = 0.71). There were no statistical differences in ventricular arrythmias or supraventricular (SV) arrythmias between both groups (p = 0.255 and p = 0.406 respectively) Table 4.

Table 4 Comparison of ventricular arrythmias and ICD shocks during follow-up between patients under digoxin and without digoxin

	NDG	DG	*p* value
Appropriate ICD shocks (%)	7.8 (n = 15)	8.7 (n = 9)	0.709
Ventricular arrythmias (%)	39.4 (n = 76)	32.7 (n = 34)	0.255
VF (%) **Sustained VT (%)** **Non-sustained VT (%)**	2.6 (n = 2) 3.9 (n = 3) 93.4 (n = 71)	5.9 (n = 2) 2.9 (n = 1) 91.2 (n = 31)	0.829
SV arrythmia (%)	29.5 (n = 57)	25.0 (n = 26)	0.406
AF **Auricular Flutter** **SVT**	82.5 (n =47) 7.0 (n = 4) 10.5 (n = 6)	92.3 (n = 24) 0.0 (n = 0) 7.7 (n = 2)	0.465
AF (%)	24.4 (n =47)	23.1 (n = 24)	0.806
Biventricular pacing percentage *	97.15 ± 5.18	96.53 ± 5.41	0.407

*mean ± standard deviation.

AF-= Auricular Fibrillation; BIV = Biventricular pacing; ICD = Implantable Cardiac Defibrillator; SVT = Supraventricular Tachycardia; VF – Ventricular Fibrillation.

3.2 Survival outcomes

During follow-up, global mortality, HF admissions and heart transplant rates were significantly higher in DG (global mortality: 42.3% in DG and 25.4% in NDG, p = 0.003; OR = 2.16 (IC)); HF admissions: 53% vs 35.8 %, p = 0.011; OR = 1,86 (IC)) and heart transplant: 12.5% vs 2.1%, p < 0.001, OR = 6.75(IC)). (Table 5).

Multivariate Cox proportional hazard regression analyses confirmed that digoxin was an independent predictor of all-cause mortality (HR = 1.974 ± CI 95 [1.092- 3.567], p = 0.024) , of hospitalizations due to acute HF (HR = 2.827 ± CI 95 [1.401 – 5.703], p = 0.004) and also of

any CV hospitalization (HR = 1.781 ± CI 95 [1.087 – 2.918], *p* = 0.022). (Table 5, Figure 2 to 5).

Digoxin is also an independent predictor of the combined endpoint of CV hospitalization, heart transplant and all-cause mortality (HR = 1.155 ± CI 95 [1.003 – 2.407], *p* = 0.049).

Table 5 Comparison of clinical evolution between DG and GND

	NGD	**DG**	***p* value**
CV hospitalizations (%)	35.8 (n = 69)	53.0 (n = 53)	0.011
Number of hospitalizations *	0.65 ± 1.16	1.06 ± 1.47	0.015
Hospitalization cause (%) **Heart failure** **ICD shocks or complications**	 60.3 (n = 41) 39.7 (n = 27)	 71.2 (n = 37) 28.8 (n = 15)	0.216
Heart transplant (%)	2.1 (n = 4)	12.5 (n = 13)	<0.001
Emergency admissions	27.1 (n = 51)	31.7 (n = 32)	0.231
Global mortality (%)	25.4 (n = 49)	42.3 (n = 44)	0.003
Composite of Hospitalizations or heart transplant or global mortality (%)	48.2 (n = 93)	67.3 (n = 70)	0.002
Composite of Hospitalization because HF or heart transplant (%)	21.2 (n = 41)	35.6 (n = 37)	0.007

*mean ± standard deviation.

CV = Cardiovascular; ICD = Implantable Cardio Defibrillator.

Table 6 – Impact of digoxin in mortality, hospitalization, cardiac transplant and arrythmias.

	HR	**CI**	***p* value**
All – cause mortality	1.974	1.092 – 3.567	0.024
CV hospitalizations	1.781	1.087 – 2.918	0.022
HF Hospitalizations	2.827	1.401 – 2.018	0.004
Heart transplant	6.687	0.745 – 59.91	0.090
Supraventricular arrythmias	1.721	0.895 – 3.307	0.103
Ventricular arrythmias	0.828	0.471 – 1.458	0.514
CV Hospitalizations or heart transplant or Mortality	1.155	1.003 – 2.407	0.049
HF Hospitalization or heart transplant	2.777	1.454 – 5.302	0.002

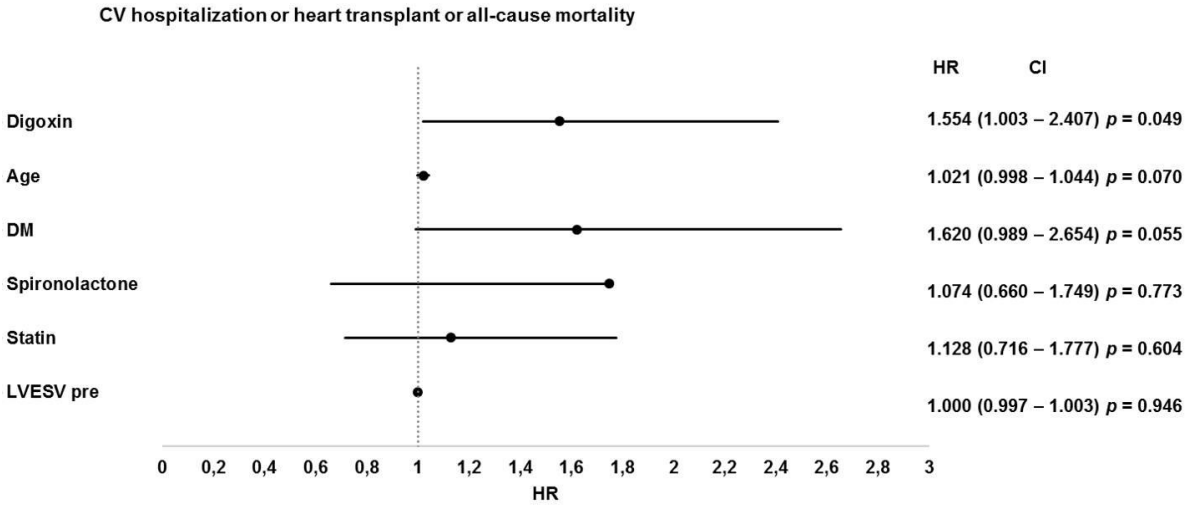

Figure 2 Forest plot of impact of digoxin in CV hospitalizations or heart transplant or mortality.

CI = Confidence interval; HF= Heart Failure; HR = Hazards Ratio. Adjust for age, digoxin, diabetes mellitus, statin, spironolactone, LVTSV pre-CRT implantation.

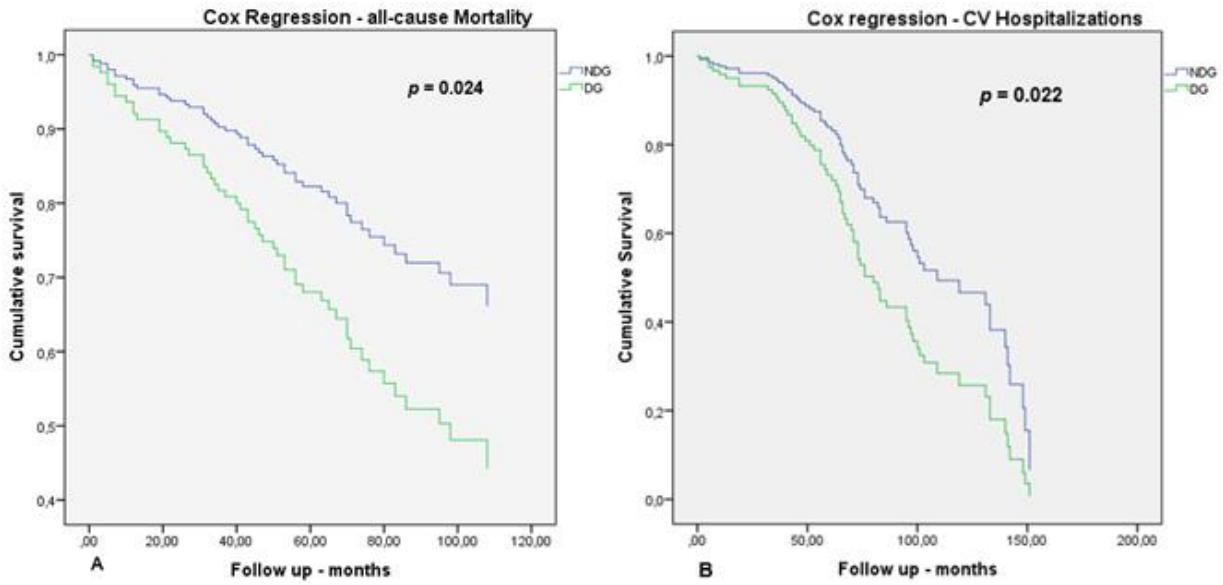

Figure 3 Survival curves for all-cause of mortality (months) (A); cardiovascular hospitalization (months) (B). Adjust for age, digoxin, diabetes mellitus, statin, spironolactone, LVTSV pre-CRT implantation.

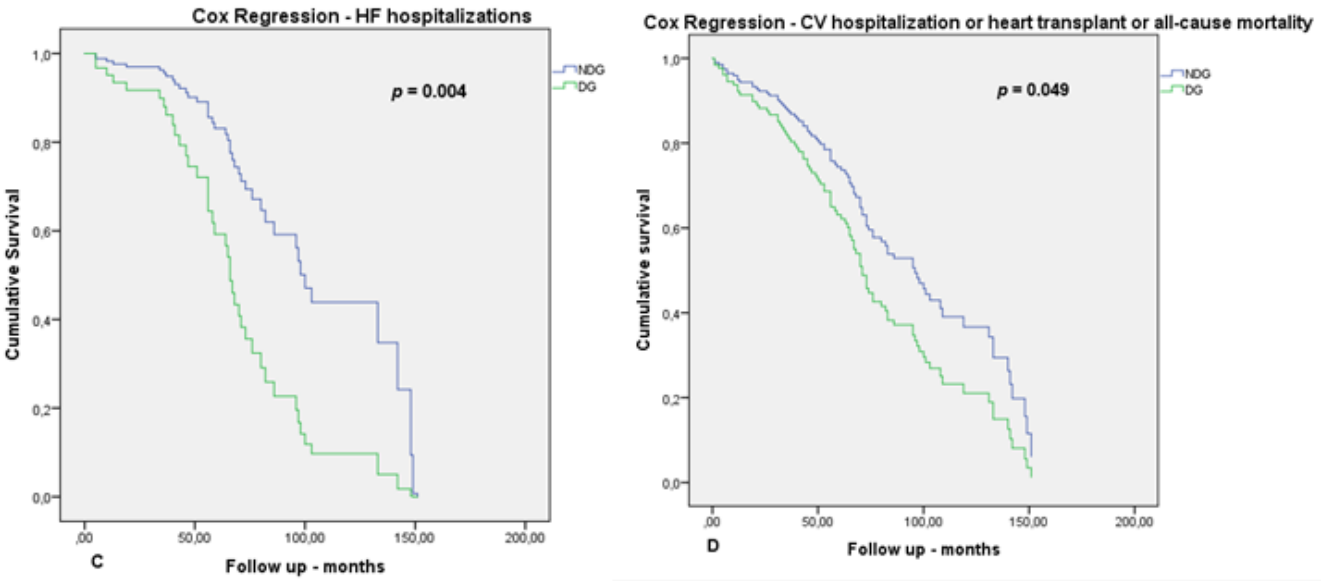

Figure 4 Heart failure hospitalization (months) (C); cardiovascular hospitalizations or heart transplant or all-cause mortality (months) (D). Adjust for age, digoxin, diabetes mellitus, statin, spironolactone, LVTSV pre-CRT implantation.

Figure 5 Heart failure hospitalizations or heart transplant (months) (E). Adjust for age, digoxin, diabetes mellitus, statin, spironolactone, LVTSV pre-CRT implantation.

4 Discussion

Digoxin have been used for many years in patients with systolic HF. In the main Digitalis Investigation Group trial (DIG), from the mid-1990s, digoxin was associated with a decreased risk of HF hospitalization, but no benefit on quality of life or mortality[11, 12].In 2014, the Cochrane Collaboration published a review on this specific topic, concluding that mortality risk remained unaffected in HF patients treated with digoxin, while the risk of readmission was reduced. However, this updated review[13], mostly reflects the ancient DIG trial and recent observational studies showed contradictory results. In fact, HF clinical trials including Val-HeFT and several observational studies have described an association between digoxin and increased mortality [14].

In the present study, digoxin was associated with a significant increased risk of death, HF hospitalization and heart transplantation during long-term follow-up of sinus rhythm patients with advanced HF submitted to CRT. Several factors can explain this difference in outcomes. The publication of DIG trial was at a time when therapy for HF was vastly different from the current contemporary care. At the time of the DIG trial, β- blockers were thought to be contraindicated in systolic HF, ACE-I (or ARB), mineralocorticoid receptor antagonists had not yet been evaluated, and CRT was a nascent technology. The use of defibrillators for primary prevention of sudden cardiac death had not been prospectively studied.

Nowadays, β- blockers are one of the more impotant drugs used in the treatment of HFrEF, being a class Ia recommendation in ESC guidelines due to its benefit on reducing mortality and morbidity[1]. It is possible that the introduction of β- blockers as a first line for HF could have changed the impact of digoxin, reducing its benefit[15]. Katz. A *et. Al* reported that the concomitant use of β-blocker and digoxin is related with a lower 1 – and – 10-year mortality risk when compared to use of digoxin alone. They also showed that digoxin use without β-blockers was associated with an increase in adjusted 1-year and 10-year mortality [16]. Of note, 88.6% of our study population was under β-blockers.

A potential mechanism to explain the high long-term mortality rate with digoxin is the proarrhythmic effect mediated by inhibition of the Na^+/K^+ adenosine triphosphatase pump in cardiac myocytes. By reducing the efflux of cytosolic Na^+, the Na^+/Ca^{2+} antiporter is inhibited and intracellular Ca^{2+} increases, facilitating ectopy through delayed afterdepolarizations and automaticity leading to the proarrhythmic potential[3, 17]. However, in our study, this potential proarrhythmic risk does not seem to explain the higher mortality in digoxin users, since we do not observe an increase in the incidence of appropriate ICD shocks or ventricular arrhythmias in patients receiving digoxin. β-blockers, mainly nonselective, that attenuate stress-induced reductions in serum potassium might neutralize the risk of arrhythmic death associated with the use of digoxin[18].

Another possible mechanism to explain the poorer prognosis in patients under digoxin, is the narrow therapeutic window. In the DIG trial, for example, digoxin levels >1.2 ng/ml were associated with increased cardiovascular mortality[3, 11, 17]. The continued use of digoxin in elderly patients, with impaired kidney function, may result in higher serum digoxin concentration [18].

In addition, it has been proposed that digoxin-mediated increase in vagal tone, reduced AV-node conduction, and shortening of atrial refractory periods may render the atrium more susceptible to AF[20]. However, in our study, we did not verify an increase incidence of AF in the digoxin group, despite the long-term follow-up.

Regarding comorbidities, in our population we found no significant differences in prevalence between patients treated with digoxin or not. However, patients taking digoxin where younger what is surprising taking in count the higher mortality rate. We may speculate, that in our study, HF patients treated with digoxin had a more advanced disease at baseline that non-digoxin users and consequently a higher risk of mortality even before digoxin treatment was started. This hypothesis is supported by the higher rate of spironolactone use in digoxin patients. However, in the multivariate analysis, even after adjustment for parameters of advanced HF (as spironolactone and LVESV), digoxin was identified as an independent predictor of poor outcomes.

Regarding the association between digoxin and the arrhythmic risk, MADIT-CRT trial assessed the impact of digoxin therapy on the risk of ventricular tachycardia (VT)/ ventricular fibrillation (FV) and AF, in ICD and CRT-D patients. They found a significantly increased risk of VT/ FV and no difference in AF [9]. Regarding ICD shocks, Mina. G *et al.* found an increased incidence of shocks (appropriated and inappropriate) and electrical storms in patients prescribed with digoxin [5]. Indeed, Desai *et al.* found an increased incidence of appropriated ICD shocks in patients with HF treated with CRT-D and digoxin [8]. Moreover, Adelstein *et al.* evaluated the association between digoxin use and appropriated tachyarrhythmia therapy in patients with CRT-D with advanced HF, verifying an increased risk of appropriated shock, more evident for those with lower baseline LVEF [21]. Soliman *et al.* found that digitalis therapy was independently and strongly related to appropriate ICD therapy [22]. In the present study, digoxin was not associated with increased risk of AF development. Moreover, we found no between digoxin use and appropriated device shocks. These differences are probably related with the fact that we included patients with all NYHA class, both ischemic and non-ischemic HF ethology, and a higher percentage of patients β-blockers.

Limitations

We acknowledge several limitations to our data. This is a single-centre retrospective analysis. To mitigate this, we included consecutive patients and a large follow up was

performed. Data on serum digoxin levels during the period of the study was not available. Finally, reverse remodelling and its relation to arrhythmias were not assessed.

5 Conclusion

Patients with advanced HF in sinus rhythm, submitted to CRT seems not benefit from digoxin as part of optimal medical therapy. The use of digoxin seems to be an independent predictor of all-cause mortality, and hospitalizations due to acute heart failure. Given the potential harm of digoxin in advanced HF patients in sinus rhythm, prospective reappraisal of digoxin's role in current era of modern HF therapy is warranted.

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