Use of digitalis in the treatment of heart failure: data from the Italian Network on Congestive Heart Failure (IN-CHF)

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Background. **Since the large multicenter DIG trial has shown no effects of digitalis on the all-cause mortality of patients with chronic heart failure (HF), the broad prescription of this drug in patients with HF appears to be at the very least, questionable. The aims of this study were: to analyze prescription patterns of digitalis, from 1995 to 2000, in a large group of outpatients with HF; to analyze the independent predictors of digitalis prescription and to evaluate the impact of the results of the DIG trial on the prescription rate of this drug.**

Methods. **From 1995 to 2000, 11 070 HF outpatients (mean age 64 ± 12 years, ejection fraction 35 ± 12%) were enrolled in a large Italian database.**

Results. **Out of 11 070 patients, 7198 (65%) were treated with digitalis. At multivariate analysis, the following variables were independently associated with digitalis prescription; atrial fibrillation (odds ratio [OR] 3.3, 95% confidence interval [CI] 2.9-3.8), ejection fraction < 30% (OR 1.7, 95% CI 1.5-1.9), NYHA class III-IV vs II-III (OR 1.3, 95% CI 1.2-1.5), admission for HF during the previous year (OR 1.4, 95% CI 1.2-1.5). After the publication of the DIG trial, there was a significant reduction in the rate of digitalis prescription: the percentage of patients taking digitalis fell from 68% in 1996-1997 to 61% in 1998-1999 (p < 0.001).**

Conclusions. **Over 60% of Italian outpatients with HF were treated with digitalis; as expected, patients with a low ejection fraction, atrial fibrillation and in a more advanced stage of HF are more likely to receive this drug. Finally, after the publication of the DIG trial, the rate of digitalis prescription significantly decreased.**

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Introduction

Although cardiac glycosides have been used for at least two centuries in the treatment of heart failure (HF), their role in the long-term management of outpatients is still debated. Evidence from clinical studies published in the last few years did not diminish the intensity of controversy. Advocates of digitalis have argued that the drug should be used because of its effectiveness in improving symptoms, quality of life and exercise tolerance in patients with HF regardless of the underlying rhythm, etiology and concomitant therapy[1-6]. Opponents of digitalis have argued that the drug should be avoided, because of doubts not only about its efficacy, but also about its safety[7,8]. The Digitalis Investigation Group (DIG) trial[9], the largest randomized, placebo-controlled study ever conducted in patients with HF to evaluate the long-term effects of digoxin on morbidity and mortality, showed that this drug provides a substantial benefit in reducing hospitalizations for HF. However, it did not modify mortality. These findings differ from those obtained with other oral agents with inotropic properties that have been associated with an adverse effect on mortality. The study presented some methodological flaws that could partially explain the neutral results on mortality observed in this trial. In fact, most of the patients enrolled in this trial were in NHYA class I-II (nearly 67%). Further, a large number of deaths and hospitalizations for worsening HF were observed in patients receiving digoxin before the start of the trial and then randomized to the placebo arm (the digoxin withdrawal group). In addition, little attention was paid to the dose titration of digoxin, thus exposing patients to the acute electric and hemodynamic complications possibly due to an

initial overdosing of digitalis[10]. Finally, a recent rebuttal by Yusuf[11] stated that physicians could avoid 52 cases of hospitalization by treating 1000 patients with digoxin for 1 year rather than 9, as was originally stated by Packer[12]. The initial figure postulated by Packer may have contributed to the reluctance of physicians in prescribing this drug.

The aims of this study were: to analyze the prescription patterns of digitalis in a large group of outpatients with HF enrolled in the Italian Network on Congestive Heart Failure (IN-CHF) registry; to analyze the independent predictors of digitalis prescription in clinical practice and to evaluate the impact of the results of the DIG trial on the prescription rate of this drug.

Methods

Data sources. Data for the present analysis derive from the IN-CHF, a registry of outpatients with HF. Since March 1995, 151 Cardiology Centers distributed across the whole country have been collecting data on outpatients with HF diagnosed in accordance with the European Society of Cardiology guidelines[13]. The main task of the IN-CHF registry was to set up a national database which could be useful for the evaluation of the clinical epidemiology of patients with HF in Italy including the management strategies.

Clinicians at the participating IN-CHF Centers were specifically trained to collect clinical and epidemiological information on outpatients with HF with the help of a software specifically prepared by the Research Center of the Italian Association of Hospital Cardiologists (ANMCO). Periodically, data were transferred to ANMCO by floppy disk or e-mail and pooled in a single database at the ANMCO Research Center.

Study population. We analyzed data collected between 1995 and 2000. Demographic, clinical, instrumental and laboratory variables and information on drug therapy were collected for each patient. When multiple etiological factors were present, the responsible cardiologist had to select the primary etiological factor. Coronary angiography and other physical examinations were performed at the discretion of the attending physician; no fixed clinical algorithm was followed in delivering care during the study. Drug use was assessed for each patient at the time of enrollment, and any additions or changes in drug treatment were monitored over a period of time for the following classes of drugs; β-blockers, calcium channel blockers, ACE-inhibitors, cardiac glycosides, diuretics, oral anticoagulants, nitrates, amiodarone, antiarrhythmic agents and other cardiovascular drugs.

Digitalis prescription analysis. To evaluate the impact of the results of the DIG trial published in 1997, we analyzed the rate of prescriptions of digitalis observed in 1996-1997 vs that of 1998-1999. The analysis of digitalis prescription was stopped in 1999 since one of the aims of this study was to evaluate the impact of the publication of the DIG trial on the prescription pattern of the drug.

Statistical analysis. Data were analyzed using the SAS statistical package. Continuous variables are expressed as mean ± SD and compared using the Student's t-test. The χ^2 test was used to evaluate the association of digitalis prescription with several baseline dichotomic characteristics. A level of $p < 0.05$ was considered as statistically significant. A logistic regression model was used to determine the independent predictors of digitalis prescription. Results are expressed as odds ratios and the relative 95% confidence interval.

Results

Demographic and clinical characteristics of the study population. Between 1995 and 2000 the 151 participating Centers enrolled 11 070 outpatients with HF.

The demographic and clinical characteristics of the study population are summarized in table I.

Digitalis was prescribed to 7198/11 070 patients (65%). Patients treated with digitalis were significantly older and with more advanced disease than those to whom this drug was not prescribed: they were more frequently in NYHA class III-IV, with a significant lower mean ejection fraction and systolic blood pressure and more frequent admission for HF during the previous year. As expected, the percentage of patients with atrial fibrillation was higher in the group treated with digitalis. Among patients treated with digitalis the most frequent etiology was idiopathic whereas ischemic heart disease was less represented. Data on serum creatinine levels were available for 6041 patients. Among these, 163 (2.7%) had an impaired renal function as defined by a creatinine level > 2.5 mg/dl. The percentage of patients with renal dysfunction and treated with digitalis was significantly lower than that found in the non-treated group. Renal impairment did not affect the dosage of the drug that was similar in patients with or without elevated serum creatinine levels (0.16 ± 0.15 vs 0.19 ± 0.11 mg, p = NS). The type of digitalis most frequently used was digoxin which was administered to 6232 patients (86.6%) while 963 patients were treated with methyldigoxin (13.4%). The mean daily dose of digoxin was 0.19 ± 0.09 mg/die (range 0.05-2.00 mg/die), while the mean daily dose of methyldigoxin was 0.18 ± 0.24 mg/die (range 0.05-2.00 mg/die). Table II shows the prescription pattern at baseline. Among patients treated with digitalis, ACE-inhibitors, diuretics and oral anticoagulants were significantly more prescribed, while β-blockers were less used. In this group, as would be

Table I. Demographic and baseline characteristics of the population.

	Digitalis		p	All cases (n = 11 070)
	Not treated (n = 3872)	Treated (n = 7198)		
Age (years)	63 ± 13	64 ± 12	< 0.0001	64 ± 12
≥ 70 (%)	33.9	36.4	0.009	35.5
Female gender (%)	25.2	28.1	0.0012	27.1
NYHA class III-IV (%)	20.7	34.7	< 0.0001	29.8
Etiology (%)				
Ischemic heart disease	46.1	36.4	< 0.0001	39.8
Dilated cardiomyopathy	25.2	34.1		31.0
Hypertensive	14.2	12.2		12.9
Other	14.6	17.3		16.3
HR ≥ 100 b/min (%)	6.1	13.8	< 0.0001	11.1
SBP < 100 mmHg (%)	2.5	3.8	0.0005	3.3
Third heart sound	17.1	26.4	< 0.0001	23.2
Ejection fraction < 30% (%)	24.0	37.7	< 0.0001	33.0
Atrial fibrillation/atrial flutter (%)	8.9	28.6	< 0.0001	21.7
Creatinine > 2.5 g/dl (%)	4.2	2.0	< 0.0001	2.7
At least one admission for HF during the previous year (%)	48.1	60.8	< 0.0001	56.3

HF = heart failure; HR = heart rate; NYHA = New York Heart Association; SBP = systolic blood pressure.

Table II. Prescription patterns at baseline.

	Digitalis		p	All cases (n = 11 070)
	Not treated (n = 3872)	Treated (n = 7198)		
ACE-inhibitors (%)	76.0	83.4	< 0.0001	80.8
β-blockers (%)	23.6	14.9	< 0.0001	17.9
Diuretics (%)	68.1	91.8	< 0.0001	83.5
Oral anticoagulants (%)	15.7	31.7	< 0.0001	26.1
Antiplatelets (%)	42.4	31.5	< 0.0001	35.3
Statins (%)	7.6	4.2	< 0.0001	5.4
Nitrates (%)	40.3	39.0	NS	39.5
Calcium channel blockers (%)	17.4	10.7	< 0.0001	13.0
Amiodarone (%)	19.3	20.1	NS	19.8
Antiarrhythmics (%)	2.8	1.8	0.0006	2.1

expected in view of the lower percentage of patients with an ischemic etiology, antiplatelets, calcium channel blockers and statins were less used. No differences in the use of nitrates were found between the two groups.

After adjustment for all the variables significantly associated with digitalis use at univariate analysis, the independent predictors of the use of this drug were found to be: atrial fibrillation, a lower ejection fraction and systolic blood pressure, an advanced NYHA class, older age and a previous hospitalization for HF (Table III). Renal dysfunction and ischemic etiology were found to be independently associated with a lower rate of digitalis prescription.

Temporal pattern in digitalis prescription. The use of digitalis over time is shown in table IV. Over the years, the use of digitalis gradually decreased from 69.6% in 1995 to 59.4% in 1999, equivalent to an absolute reduction of 14.6% in the prescription rate of this drug. When the use of digitalis was analyzed in two periods of time (1996-1997 vs 1998-1999), the percentage of patients treated with digitalis fell from 68% in 1996-1997 to 61% in 1998-1999 ($p < 0.001$) (Fig. 1). In the same period, we observed a progressive rise in the rate of β-blocker prescriptions: from 7% in 1995, to 24.7% in 1998 ($p < 0.001$) while the prescription rate of ACE-inhibitors remained unchanged (from 81% in 1995 to 79% in 1999, p = NS).

Table III. Independent predictors of digitalis prescription.

	OR	CI 95%	p
Atrial fibrillation	3.34	2.92-3.81	< 0.0001
Ejection fraction < 30%	1.71	1.51-1.93	< 0.0001
Third heart sound	1.48	1.33-1.65	< 0.0001
Cardiothoracic ratio	1.41	1.09-1.83	0.009
NYHA class III-IV	1.40	1.26-1.54	< 0.0001
Ventricular tachycardia	1.38	1.12-1.70	0.003
Admission for HF in the previous year	1.36	1.25-1.48	< 0.0001
Heart rate	1.017	1.014-1.020	< 0.0001
Age (as continuous variable)	1.008	1.004-1.010	< 0.0001
SBP (as continuous variable)	0.994	0.992-0.996	< 0.0001
Coronary heart disease	0.70	0.64-0.79	< 0.0001
Creatinine > 2.5 mg/dl	0.43	0.31-0.60	< 0.0001

CI = confidence interval; HF = heart failure; NYHA = New York Heart Association; OR = odds ratio; SBP = systolic blood pressure.

Table IV. Patients treated with digitalis from 1995 to 1999.

	1995	1996	1997	1998	1999
No. patients	2061	2397	2227	2570	1815
No. patients treated	1434 (69.6%)	1645 (68.6%)	1444 (64.8%)	1597 (62.1%)	1078 (59.4%)*

* p = 0.001.

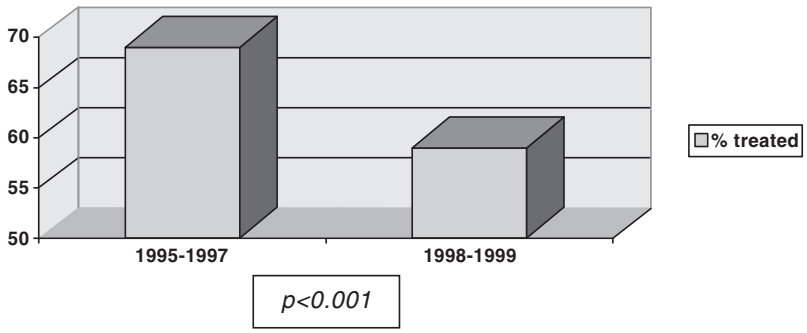

Figure 1. *Patients treated with digitalis during 1995 to 1997 vs 1998 to 1999.*

Discussion

In the last few years many trials have been conducted to identify therapies able to improve the prognosis of patients with HF; the results of these trials have been critically reviewed, simplified and summarized by expert panels into guidelines outlining the diagnosis and management of HF[14]. These guidelines recommend digoxin treatment for patients with systolic dysfunction and persistent symptoms of HF (NYHA class II-III-IV) receiving conventional pharmacological therapy with diuretics, ACE-inhibitors and β-blockers. Data from IN-CHF, reflecting the treatment policy adopted by cardiologists operating in Italian HF clinics, confirm that despite the introduction of a variety of new classes of drugs, digoxin continues to have an important role in outpatient management. In this setting, digitalis was used in roughly 65% of the observed patients. This percentage is similar to that observed for in-hospital patients admitted either in Cardiology Units (63%) or in the Medical/Generalist Units (61%)[15]. Other databases collecting data on Italian patients with HF showed a similar use: the SEOSI study[16], a survey on HF in-hospital Cardiology Units which was performed in 1997 on 3921 patients, showed that digitalis was prescribed to 62% of patients and that it was used more frequently in case of an advanced NYHA class and in patients with idiopathic cardiomyopathy.

In the TEMISTOCLE study[17], a survey performed on 2127 patients with the aim of determining the different outcomes in patients with HF hospitalized both in Medicine and Cardiology, the rate of digitalis pre-

scription was roughly similar: 71% during hospitalization and 61% at hospital discharge.

Predictors of digitalis prescription. As expected, digitalis was prescribed to more compromised patients, such as those with atrial fibrillation, a more advanced age, higher heart rate, frequent hospital admissions during the previous years, an advanced NYHA class, and those with a lower ejection fraction. These findings are in accordance with the suggestions of current international guidelines[13,18].

A significantly less frequent use of digitalis was associated with an ischemic etiology. This may be partly due to the attitude of cardiologists who tend to consider the potential dangers of this drug in the long-term treatment of ischemic HF. In fact, digitalis use was shown to be an independent predictor of death after acute myocardial infarction in two case-controlled studies[6,8]. However, these studies could not determine whether the increased risk for clinical events was due to digitalis itself or to other confounding variables that induced physicians to prescribe it[12]. In the MILIS (Multicenter Investigation of the Limitation of Infarct Size) study[19] 903 patients with myocardial infarction were enrolled. Having adjusted for the potential confounding clinical differences, digitalis therapy was not confirmed to be a risk factor for death when prescribed to patients with a myocardial infarction. Nevertheless, available data indicate that further randomized studies specifically addressing the issue of digitalis in patients with HF secondary to ischemic heart disease are needed[19].

Type of digitalis and prescribed doses. Although digoxin has an unpredictable variability in intestinal absorption due to the type of intestinal flora, the oral route remains the preferred form of administration (86.6%) of digitalis, confining the use of methyldigoxin and digitoxin to < 15% of the patients treated with digitalis. Another reason for its choice may be the fact that most trials adopted digoxin as the study treatment.

Saunders et al.[20] provided information from their database regarding prescription records for patients in the United States, France and United Kingdom. They found that the daily intake of digoxin was significantly different in the various countries, and that in the United Kingdom there was a lower prescription rate in comparison to the other two countries.

In the DIG trial[9] scarce attention was given to the appropriate doses of digitalis. In addition, the range of plasma digoxin concentrations (between 0.5-2.0 ng/dl) as well as the daily dose (the mean daily dosage in the treatment group was 0.24 mg and 81% of patients were treated with 0.25 mg or more of digoxin daily) were both wide. It has recently been suggested that low doses of digoxin may be effective and result in less toxicity. The results of a sub-study of the DIG trial demonstrate that higher serum digoxin concentrations are associated with an increased risk of all-cause mortality and of cardiovascular mortality while the mortality due to worsening HF was not affected. In this analysis, the patients were divided into three groups on the basis of their serum digoxin concentration measured 1 month after randomization: 1) 0.5 to 0.8 ng/dl, 2) 0.9 to 1.2 ng/dl, and 3) ≥ 1.2 ng/dl. After the adjusted analysis the patients in the first group showed a lower risk of all-cause and cardiovascular mortality. In contrast, patients in the second group had a mortality rate comparable to that of patients assigned to placebo. Besides, patients in the third group had a higher cardiovascular mortality[21].

Although in our database, the plasma levels of digoxin are not available, the mean daily dose of digoxin and methyldigoxin seems to be rather "low" (respectively 0.19 ± 0.09 and 0.18 ± 0.24 mg/die) with respect to the dosages used in the DIG trial.

Temporal trends in digitalis prescription. Although clinical guidelines on the treatment of HF, even after the publication of the DIG trial, consistently recommend the use of digoxin in patients in sinus rhythm to improve the clinical status of those with persisting HF symptoms due to left ventricular systolic dysfunction despite ACE-inhibitor and diuretic treatment, in patients with atrial fibrillation and in those with "any degree of symptomatic HF"[22,23], it is important to note that our study has shown a significant reduction in digitalis prescription, which fell from 69.6 to 59.4% in the time interval between 1996 and 1999. This fact could reflect the Italian cardiologist's perception of the neutral effect of this drug in reducing the mortality of patients with HF. This reluctant attitude of Italian cardiologists may be also supported by the doubts raised in the DIG trial regarding the true efficacy of digitalis in avoiding hospitalizations. In fact, the 28% reduction in hospitalizations for HF, although significant, is so small that physicians would avoid only 9 events by treating 1000 patients with digoxin for 1 year[4]. However, a re-analysis of the data by Yusuf[11] demonstrated that these estimates were incorrect. The estimate by Packer[12] probably did not take into consideration the number of multiple hospitalizations and the adjustments for the actual duration of digoxin use in the two groups. In this report treatment with digoxin was associated with 53 fewer hospitalizations per 1000 patients/years of treatment.

Another key issue in interpreting the decreased use of digitalis is the concomitant and rapid increase in the use of β-blockers. Recently, β-blocker therapy has become a cornerstone of therapy for HF and its use is rapidly increasing all over the world. Accordingly, even our database demonstrated that the use of β-blockers increased from 7% in 1995 to 25% in 1998. If the decrease in the prescription of digitalis by cardiologists in Italy is the expression of a progressive replacement of this drug by a β-blocker, this finding must not be seen as a negative phenomenon because both agents modu-

late neurohormonal activation but β-blockers showed a higher mortality/morbidity reduction than digitalis in the treatment of HF due to any etiology.

In conclusion, in the setting of the Italian HF clinics, digitalis still remains a therapeutic tool in patients with more advanced stages of HF. Nevertheless, there has been a significant reduction in its use. This may be either due to a concomitant increase in the use of β-blockers or to a decreased reliance on its efficacy after the publication of the DIG trial.

Appendix

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