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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Digoxin and mortality in atrial fibrillation: a prospective cohort study

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Abstract
Objective The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study showed that rhythm-control treatment of patients with atrial fibrillation (AF) offered no survival advantage over a rate-control strategy. In a subgroup analysis of that study, it was found that digoxin increased the death rate [relative risk (RR)= 1.42), but it was suggested that this may have been attributable to prescription of digoxin for patients at greater risk of death, such as those with congestive heart failure (CHF). No study has investigated a priori the effect of digoxin on mortality in patients with AF. This study aimed to address this question.
Methods Using data from the Registry of Information and Knowledge about Swedish Heart Intensive care Admissions (RIKS-HIA), we studied the 1-year mortality among patients admitted to coronary care units with AF, CHF, or AF+CHF with or without digoxin (n=60,764) during 1995–2003. Adjustment for differences in background characteristics and other medications and treatments was made by propensity scoring.
Results Twenty percent of patients with AF without CHF in this cohort were discharged with digoxin. This group had a higher mortality rate than the corresponding group not given digoxin [adjusted RR 1.42 (95% CI 1.29–1.56)], whereas no such difference was seen among patients with CHF with or without AF, although these patients had a nearly three-times higher mortality.
Conclusion The results suggest that long-term therapy with digoxin is an independent risk factor for death in patients with AF without CHF.

Keywords Digoxin · Atrial fibrillation · Heart failure · Mortality · RIKS-HIA

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Introduction

Digoxin is widely used in clinical practice for treatment of congestive heart failure (CHF) and atrial fibrillation (AF). Whereas the efficacy of digoxin in AF has been disputed, the drug's beneficial effects in CHF include reduced symptoms, improvement in New York Heart Association (NYHA) class, increased exercise time, modestly increased left ventricular ejection fraction (LVEF), increased cardiac output, and decreased CHF hospitalizations [6, 13, 36]. Furthermore, digoxin withdrawal has been found to be associated with an increased hospitalization rate and decreased LVEF [22, 37].

The Digitalis Investigation Group (DIG) trial tested the effect of digoxin versus placebo on survival in 7,788 patients with CHF and normal sinus rhythm [1]. In both treatment groups, the all-cause mortality was 35% and cardiovascular mortality 30%. There was a trend toward decreased mortality caused by CHF in the digoxin group, but this was offset by an increase in deaths from other causes that included deaths presumed to result from arrhythmias. Whereas the trial showed that digoxin reduced

the risk of hospitalization because of worsening CHF [1], confirming the results of previous trials [22, 37], the drug did not appear to influence the quality of life [18].

Digoxin is also commonly used for the treatment of AF, although no trial has tested the effect of digoxin on mortality in this indication. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study [41] showed that use of a rhythm-control strategy in the treatment of patients with AF offered no survival advantage over a rate-control strategy, but at the same time, it was found by chance in a later subgroup analysis that digoxin appeared to increase the death rate [relative risk (RR)= 1.42] [5]. It was suggested that this may have been attributable to prescription of digoxin for patients at greater risk of death, such as those with congestive heart failure, but this could not be proven. Thus, further studies are needed to test the effect of digoxin on mortality in patients with AF. In the present study, we investigated the 1-year mortality rate among patients admitted to coronary care units in Sweden with AF, CHF or AF+CHF during a 9-year period and those prescribed or not prescribed digoxin with the aim of testing the effect of long-term digoxin treatment on mortality in patients with AF compared with those with CHF. This study is the first to investigate the effect of digoxin on mortality in maintenance therapy of AF, despite the drug having been used in that indication for over a century.

Methods

This was a cohort study. Data for the study patients were obtained from the Registry of Information and Knowledge about Swedish Heart Intensive care Admissions (RIKS-HIA), for the period between January 1995 and December 2003. RIKS-HIA contains prospectively collected and detailed information on all patients admitted to most coronary care units at Swedish hospitals, as previously described [34]. We obtained 1-year mortality data by combining information from the RIKS-HIA database with that from the National Cause of Death Registry, which includes the vital status of all Swedish citizens. The register and the merging with registries were approved by an ethics committee and the National Board of Health and Welfare.

Inclusion/exclusion criteria

An overview of the inclusion of patients is given in Fig. 1. The study subjects consisted of three categories: (a) patients with AF, (b) patients with CHF, and (c) patients with AF +CHF. The AF group consisted of patients with an electrocardiogram (ECG) finding of AF on admission or at discharge, and patients with a discharge diagnosis of AF [International Center for Disease Control (ICD) 10 I48] without a concomitant diagnosis of CHF or pulmonary edema. The CHF group consisted of patients with a medical

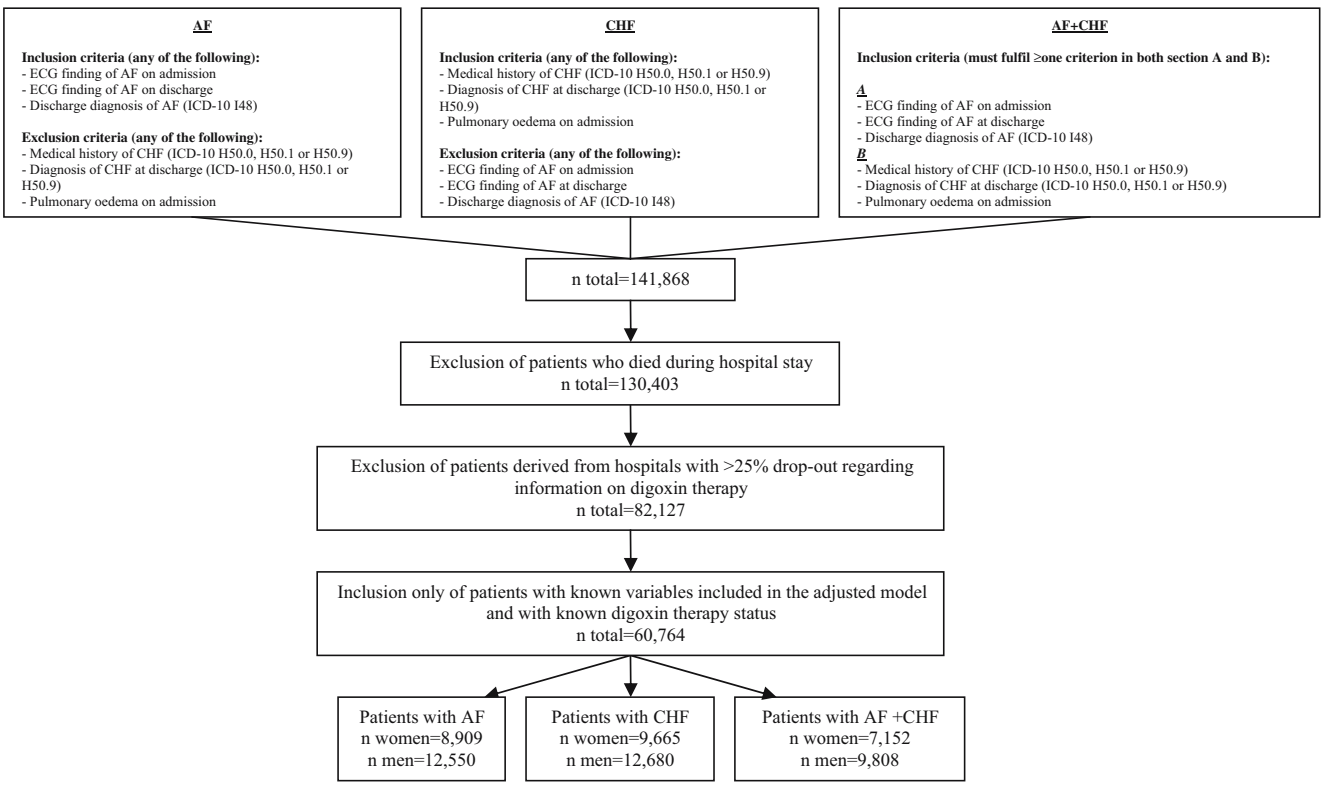

Fig. 1 Inclusion of study patients registered in Registry of Information and Knowledge about Swedish Heart Intensive care Admissions (RIKS-HIA) during the period January 1995 to December 2003

history of CHF, a diagnosis of CHF at discharge (ICD 10 H50.0, H50.1, or H50.9), or pulmonary edema on admission without concomitant AF. The AF+CHF group consisted of patients with an ECG finding of AF on admission or at discharge or patients with a discharge diagnosis of AF, with a concomitant medical history of CHF, a diagnosis of CHF at discharge, or pulmonary edema on admission. Patients who died during their hospital stay were excluded from the analyses. This was done because this was a study of the long-term effect of digoxin on mortality, so that patients who were the most likely to have died due to other reasons, i.e., due to cardiac disease per se quickly after being admitted to hospital, were excluded. Information on digoxin therapy was lacking in 20% of the cases but varied considerably between reporting hospitals. Therefore, only patients with a known digoxin therapy status derived from hospitals with missing data for <25% regarding digoxin therapy were included, giving a total number of 82,127 patients.

Statistical analyses

The AF, CHF, and AF+CHF groups were each divided into two subgroups according to digoxin therapy. The 1-year mortality rates following admission to the coronary care unit were determined for each category and compared between those who were prescribed digoxin and those who were not. A further division by sex was also made, as a sex-based difference in mortality among patients taking digoxin has been reported [25]. The average relative risk (RR) of death in patients discharged with digoxin compared with those without digoxin was estimated using Cox regression analysis. Separate estimates of RR were also calculated for men and women. Since this was not a randomized controlled clinical trial, we did not know each patient's probability of receiving digoxin therapy as we would have done otherwise. To estimate these probabilities and account for baseline heart disease severity, we applied a propensity score method [27] using logistic regression analysis. Propensity scoring is a well-established method used in cohort studies such as this one and has been used extensively [4, 19, 20, 38]. Similar propensity score methods have also been applied in other studies of data from the RIKS-HIA database [32–35]. Simply put, propensity score is a measure of the likelihood that a patient would have been treated using their covariate scores and can be thought of as a balancing score [28]. By using the probability that a subject would have been treated (the propensity score) to adjust the estimate of the treatment effect, we created a quasiexperiment, mimicking a randomized trial. For instance, we find two subjects with the same propensity score, one treated, one a control. We can think of these two subjects as "randomly assigned" to each group, since they have the same probability of being in either group, given their covariates. Thus, propensity scores summarize all the information from the covariates in one single number, namely, the probability of being assigned to the treatment given the covariates and thereby offer advantages over more common methods of adjustments, especially if the adjustments involve a large number of covariates. Propensity scores can be used, along with variables that could not be balanced, as predictors in a regression model. Separate regressions can be fitted by propensity score quintile to estimate the treatment effect within quintile, as well as the overall treatment effect. The total number of patients available for complete case analyses in the adjusted model was 60,764 (AF=21,459, CHF=22,345, AF+CHF=16,960). The variables included in the logistic regression analysis were: age, sex, smoking status, diabetes mellitus, hypertension, medications on admission [angiotensin-converting enzyme (ACE) inhibitors, diuretics, nitroglycerin, beta-blockers, acetylsalicylic acid/platelet inhibitors, lipid-lowering drugs, anticoagulant drugs], history of CHF, admission ECG (ST elevation, left bundle branch block), pacemaker, and continuous positive airway pressure (CPAP). Several two-way interactions were included after selection by a stepwise procedure using the Akaike information criteria (AIC) for inclusion/exclusion. All included variables and interactions are shown in Table 1. When analyzing possible sex-based differences, sex was excluded from the propensity score. The propensity score was then entered, together with digoxin and other discharge treatments (ACE inhibitors, diuretics, nitroglycerin, beta-blockers, acetylsalicylic acid/platelet inhibitors, lipid-lowering drugs, anticoagulant drugs) in the Cox regression analysis to adjust for differences between the digoxin and nondigoxin patients regarding the variables listed above. We thus compared patients with a similar probability of receiving digoxin to distinguish between the risk of having digoxin treatment and the risk of having the indication for which digoxin was given. For all statistical analyses R, version 2.2.1 (R foundation for Statistical Computing, Vienna, Austria) was used. As of 1999, registration of data on LVEF was voluntary, and serum (s-)creatinine was introduced as a compulsory variable at the end of 2002. These two variables, known to be associated with mortality [10, 23], were therefore not included in the propensity score. However, in patients for whom data on LVEF and s-creatinine were available, we tested whether they still affected mortality beyond the variables already included in the propensity score. This was done by comparing the RR of death between patients prescribed and those not prescribed digoxin among patients with LVEF<30% and LVEF>30% and among patients with s-creatinine values that were low [<85 μmol/l (female), <95 μmol/l (male)], normal [85–105 μmol/l (female), 95–115 μmol/l (male)], or

Table 1 Variables and interactions included in the propensity score model

List of variables and interactions
Variables
Demographics
Age
Sex
Risk factors
Smoking
Diabetes mellitus
Hypertension
Previous myocardial infarction
History of congestive heart failure
History of PTCA/CABG
Therapy before entry
Acetylsalicylic acid/platelet inhibitor
Beta-blocker
Diuretic
Lipid-lowering drug
Long-acting nitrate
Anticoagulant therapy
ECG on admission
Pacemaker rhythm
Left bundle branch block or ST elevation
No left bundle branch block or ST elevation
Treatment during hospital stay
CPAP
Interactions
Age: history of congestive heart failure
Age: diuretics before entry
Age: ACE inhibitor before entry
Age: long-acting nitrate before entry
Age: anticoagulant therapy before entry
Age: CPAP during hospital stay
Age: left bundle branch block or ST elevation on admission
Age: no left bundle branch block or ST elevation on admission
Age: pacemaker rhythm
Left bundle branch block or ST elevation on admission: beta-blocker before entry
No left bundle branch block or ST elevation on admission: beta-blocker before entry
Left bundle branch block or ST elevation on admission: CPAP during hospital stay
No left bundle branch block or ST elevation on admission: CPAP during hospital stay
Left bundle branch block or ST elevation on admission: smoking
No left bundle branch block or ST elevation on admission: smoking
Sex: smoking
Sex: age
Sex: CPAP during hospital stay
Sex: hypertension
Sex: lipid-lowering drug before entry
Sex: history of congestive heart failure
Sex: history of PTCA/CABG
Diuretics before entry: hypertension
Beta-blocker before entry: pacemaker rhythm
Beta-blocker before entry: ASA/platelet inhibitor before entry
Beta-blocker before entry: previous myocardial infarction
Beta-blocker before entry: smoking
History of congestive heart failure: beta-blocker before entry
Lipid-lowering drug before entry: beta-blocker before entry
Lipid-lowering drug before entry: hypertension
ASA/platelet inhibitor before entry: previous myocardial infarction
ASA/platelet inhibitor before entry: hypertension
History of congestive heart failure: left bundle branch block or ST elevation on admission
History of congestive heart failure: no left bundle branch block or ST elevation on admission
History of congestive heart failure: previous myocardial infarction
History of congestive heart failure: hypertension
Diabetes mellitus: CPAP during hospital stay
Diabetes mellitus: beta-blocker before entry
Diabetes mellitus: diuretics before entry
Long-acting nitrate before entry: pacemaker rhythm
Hypertension: pacemaker rhythm
Diuretics before entry: beta-blocker before entry
ACE inhibitor before entry: CPAP during hospital stay
ACE inhibitor before entry: smoking
CPAP during hospital stay: hypertension
Diuretics before entry: ASA/platelet inhibitor before entry
Long-acting nitrate before entry: pacemaker rhythm
Smoking: pacemaker rhythm
Anticoagulant therapy before entry: pacemaker rhythm
Lipid-lowering drug before entry: anticoagulant therapy before entry

ACE=angiotension converting enzyme; CPAP=continuous positive airway pressure; PTCA=percutaneous transluminal coronary angioplasty; CABG=coronary artery by-pass grafting

elevated [>105 μmol/l (female), >115 μmol/l (male)]. Also, as it has been suggested that digoxin may be harmful in patients with acute myocardial infarction (AMI) [30], we further investigated whether or not patients who had suffered AMI, defined as a discharge diagnosis of AMI, still influenced the effect of digoxin on mortality after adjustment for propensity score and for discharge treatments. This was done by comparing the RR for death between those prescribed and those not prescribed digoxin among patients with and without AMI.

Results

Unadjusted patient characteristics distributed according to whether or not patients were discharged with digoxin are shown in Table 2. After applying the propensity score, the digoxin/no digoxin groups were well balanced with respect to the collected baseline risk factors (Table 3). The likelihood of being discharged with digoxin, irrespective of digoxin therapy at the time of admission, decreased

Table 2 Unadjusted characteristics of patients discharged with and without digoxin

	ALL *digoxin at discharge*		**AF** *digoxin at discharge*		**CHF** *digoxin at discharge*		**AF+CHF** *digoxin at discharge*	
	No (*n*=44,338)	Yes (*n*=16,426)	No (*n*=16,587)	Yes (*n*=4,872)	No (*n*=18,549)	Yes (*n*=3,796)	No (*n*=9,202)	Yes (*n*=7,758)
Demographics								
Age (years)*	67/75/81	70/77/82	62/72/79	70/76/81	69/76/82	69/76/82	72/78/83	71/78/83
BMI (kg/m^2)*	23.4/25.8/28.7	22.5/24.9/27.8	23.7/25.9/28.6	23.3/25.4/28.1	23.2/25.9/29.0	22.0/24.4/27.4	23.1/25.7/28.4	22.5/24.8/27.8
Sex (% men)	58.8	54.6	60.7	51.1	56.8	56.5	59.6	55.9
Risk factors								
Smoking	13.6	12.3	12.1	11.5	17.0	15.0	9.8	11.4
Diabetes mellitus	23.3	28.4	14.2	21.1	29.4	36.1	27.5	29.2
Hypertension	39.4	38.1	36.3	38.2	41.3	39.4	41.2	37.3
Previous myocardial infarction	40.4	42.5	24.3	26.2	49.7	57.0	50.4	45.7
History of congestive heart failure	33.6	49.2	0	0	42.7	63.1	75.5	73.2
History of PTCA/CABG	7.7	6.8	6.6	5.3	8.1	8.5	9.1	6.8
Congestive heart failure at time of discharge	47.7	49.4	0	0	89.9	92.2	48.5	59.5
Ischemic heart disease	57.2	52.3	41.8	48.2	71.8	63.9	55.2	49.3
S-creatinine <85 (female), <95 (male) μmol/l	29.6	28.3	40.0	37.4	25.1	18.4	20.4	25.7
S-creatinine 85–105 (female), 95–115 (male) μmol/l	30.2	31.5	34.8	35.6	28.2	26.6	26.0	30.4
S-creatinine >105 (female), >115 (male) μmol/l	40.3	40.2	25.2	27.0	46.7	55.1	53.6	43.9
Therapy before entry								
ASA/platelet inhibitor	48.7	46.0	41.3	43.6	54.6	53.5	50.2	43.9
Beta-blocker	51.9	45.7	50.5	45.0	51.1	47.5	56.1	45.3
ACE inhibitor	32.5	41.2	17.8	21.5	38.4	52.6	47.0	47.9
Digoxin	7.6	59.4	7.3	53.9	3.6	59.4	16.1	62.9
Diuretic	48.1	65.0	27.7	43.2	54.9	72.8	71.0	75.0
Lipid-lowering drug	18.9	14.9	16.5	12.0	20.6	19.4	19.7	14.6
Long-acting nitrate	31.0	34.4	20.5	25.3	36.1	41.2	39.6	36.7
ECG on admission								
Pacemaker rhythm	2.5	3.0	1.4	1.0	3.6	7.9	2.3	1.7
ST elevation	13.8	10.3	9.3	9.8	19.8	14.8	9.8	8.4
Left bundle branch block	12.9	16.7	6.5	8.2	16.5	23.3	17.0	18.8
Index events during hospital stay								
Hypotension	5.9	6.8	3.0	3.6	8.1	10.6	6.9	6.9
Treatment during hospital stay								
IV diuretics	46.0	55.5	18.4	32.6	68.2	74.7	50.8	60.5
IV inotropics	2.5	3.5	1.1	1.4	3.6	6.6	2.8	3.3
IV nitrates	25.5	25.6	13.4	17.1	37.1	38.1	24.1	24.8
CPAP	10.5	11.7	0.6	1.7	19.9	24.9	9.1	11.4
Pacemaker	2.5	1.6	3.3	2.1	1.2	1.2	3.6	1.5
Complications								
Congestive heart failure during hospital stay	47.4	56.7	18.5	32.9	70.9	76.9	51.9	61.7
LVEF≤30%	18.5	25.8	4.2	11.3	24.1	41.8	23.5	25.9
LVEF 31–40%	24.7	25.0	10.7	15.6	31.3	30.6	26.6	27.6

Table 2 (continued)

	ALL *digoxin at discharge*		**AF** *digoxin at discharge*		**CHF** *digoxin at discharge*		**AF+CHF** *digoxin at discharge*	
	No (n=44,338)	Yes (n=16,426)	No (n=16,587)	Yes (n=4,872)	No (n=18,549)	Yes (n=3,796)	No (n=9,202)	Yes (n=7,758)
LVEF 41–50%	28.1	27.5	24.8	32.6	30.1	21.2	27.3	27.7
LVEF>50%	28.7	21.7	60.2	40.6	14.4	6.4	22.6	18.7
ST elevation	13.3	10.0	9.3	9.2	18.8	14.6	9.2	8.2
Procedures during hospital stay								
Coronary angiography	10.9	7.3	9.8	8.1	13.7	9.3	7.4	5.7
PTCA	4.6	2.8	4.5	3.4	5.7	3.4	2.9	2.2
CABG	1.6	1.3	1.3	1.4	2.2	1.6	1.1	1.0
Therapy at discharge								
ASA/platelet inhibitor	62.7	54.2	52.5	51.0	74.9	66.7	56.4	50.1
Beta-blocker	70.9	59.3	68.9	60.5	73.6	60.0	69.1	58.2
ACE inhibitor	50.7	57.0	25.2	31.7	69.1	75.4	59.6	63.7
Diuretic	63.0	80.9	32.6	55.0	83.6	93.1	82.8	90.6
Lipid-lowering drug	28.5	20.1	24.6	17.9	33.6	25.8	25.4	18.6
Long-acting nitrate	38.3	42.3	26.1	33.5	46.0	51.1	44.9	43.6
Anticoagulant therapy	19.6	33.5	22.1	34.5	11.3	19.6	31.6	39.6

Only patients with complete information on all variables included in the adjusted model are included. Values are percentages of patients unless otherwise stated

AF atrial fibrillation, *CHF* congestive heart failure, *BMI* body mass index, *ACE* angiotensin-converting enzyme, *CPAP* continuous positive airway pressure, *LVEF* left ventricular ejection fraction, *PTCA* percutaneous transluminal coronary angioplasty, *CABG* coronary artery bypass grafting, *S-creatinine* serum creatinine, *ASA* acetylsalicylic acid, *ECG* electrocardiography. Unit for s-creatinine is μmol/L.

* 25th, 50th and 75th percentiles

significantly for each year: from 37% in 1995 to 20% in 2003. Patients with AF had an overall 1-year mortality of 9.8%, compared with 23.9% for CHF and 27.3% for AF +CHF.

Patients with AF

The estimated 1-year cumulative mortality in patients with AF discharged with and without digoxin is shown in Fig. 2. Patients who were discharged with digoxin did worse than those who did not receive the drug. After adjustment, RR for death was 1.42 [95% confidence interval (CI) 1.29–1.56]. There was no statistically significant sex-based difference [RR for death among women 1.34 (95% CI 1.17–1.53) and among men 1.51 (95% CI 1.33–1.71)].

Patients with CHF

The estimated 1-year cumulative mortality in patients with CHF discharged with and without digoxin is shown in Fig. 3. Patients who received digoxin at the time of discharge did somewhat worse than those who did not receive the drug. After adjustment, RR for death was 1.11 (95% CI 1.04–1.19). There was no statistically significant sex-based difference [RR for death among women 1.04 (95% CI 0.94–1.16) and among men 1.17 (95% CI 1.07–1.28)].

Patients with AF+CHF

The estimated 1-year cumulative mortality in patients with AF+CHF discharged with and without digoxin is shown in Fig. 4. There was no difference between patients who were discharged with digoxin and those who did not receive the drug. after adjustment, RR for death was 1.00 (95% CI 0.94–1.06). No significant sex-based difference was observed [RR for death among women 1.04 (95% CI 0.95–1.14) and among men 0.98 (95% CI 0.91–1.06)].

Effects of LVEF and s-creatinine

After adjustment for propensity score and discharge treatments, neither LVEF nor s-creatinine significantly affected the RR for death between patients discharged with and without digoxin. In patients with LVEF≤30% (449 received digoxin, 1,166 did not receive digoxin) and in those with LVEF>30% (1,292 received digoxin, 5,195 did not receive digoxin), the RRs for death were 1.06 (95% CI 0.86–1.31) and 1.14 (95% CI 0.98–1.32), respectively, after adjustment. In patients with low s-creatinine (422 received digoxin, 1,635 did not receive digoxin), normal s-creatinine (469 received digoxin, 1,672 did not receive digoxin) and high s-creatinine (602 received digoxin, 2,233 did not receive digoxin), the RRs for death were 1.23 (95% CI

Table 3 Adjusted characteristics of patients discharged with and without digoxin according to propensity score quintiles

	Quintile 1 *digoxin at discharge*		**Quintile 2** *digoxin at discharge*		**Quintile 3** *digoxin at discharge*		**Quintile 4** *digoxin at discharge*		**Quintile 5** *digoxin at discharge*	
	No (*n*=10,604)	Yes (*n*=1,557)	No (*n*=9,695)	Yes (*n*=2,467)	No (*n*=9,092)	Yes (*n*=3,054)	No (*n*=8,208)	Yes (*n*=3,942)	No (*n*=6,738)	Yes (*n*=5,406)
Demographics										
Age*	56/64/73	58/67/74	69/75/80	69/75/80	73/78/83	73/78/83	73/79/84	73/79/83	71/78/83	71/77/82
Sex (% men)	74.0	72.5	63.6	62.5	52.5	52.7	47.6	48.8	50.4	50.9
Risk factors										
Smoking	19.7	18.9	13.2	12.9	11.6	10.9	10.6	11.3	11.0	11.7
Diabetes mellitus	9.8	14.0	19.5	19.6	25.3	25.5	33.9	32.3	34.6	35.2
Hypertension	33.5	36.7	44.1	44.6	44.8	44.0	41.9	41.6	31.5	29.5
Previous myocardial infarction	31.3	33.9	40.3	40.6	44.5	44.4	42.8	42.5	46.0	44.8
History of congestive heart failure	4.0	4.4	18.9	19.1	34.7	35.5	50.0	50.1	79.5	82.8
History of PTCA/CABG	11.0	10.6	8.0	7.9	6.6	6.3	6.1	6.3	5.7	5.6
Congestive heart failure at time of discharge	33.2	36.5	44.3	40.7	52.1	46.4	55.1	49.9	60.7	58.5
Ischemic heart disease	50.6	48.2	61.1	56.5	62.3	55.7	58.9	53.0	52.4	49.3
Therapy before entry										
ASA/platelet inhibitor	44.9	46.3	53.6	53.5	55.3	55.5	49.7	49.6	38.0	34.5
Beta-blocker	54.3	54.4	62.1	61.2	59.8	59.1	48.8	48.2	26.9	26.8
ACE inhibitor	14.6	15.7	26.4	26.4	35.3	35.3	40.7	41.5	55.7	58.3
Digoxin	2.6	29.9	5.0	42.5	7.1	52.4	10.2	63.8	16.4	76.5
Diuretic	7.4	9.4	35.0	34.9	54.6	54.4	71.3	72.9	93.7	95.2
Lipid-lowering drug	29.0	28.8	22.7	22.3	15.1	14.5	13.4	13.5	9.4	8.9
Long-acting nitrate	18.2	19.4	30.7	30.2	35.9	36.0	36.3	36.5	38.3	38.2
ECG on admission										
ST elevation	22.7	22.3	14.7	15.0	10.9	10.4	8.5	8.0	5.3	5.3
Left bundle branch block	5.0	5.7	10.7	9.9	13.9	14.8	16.9	16.1	22.2	24.3
Treatment during hospital stay										
IV diuretics	31.6	50.6	44.7	53.4	51.4	56.0	53.1	55.5	54.5	57.7
IV inotropics	2.6	4.7	2.3	4.1	2.5	3.3	2.4	2.9	2.8	3.6
IV nitrates	22.3	24.5	27	27	27.9	27.7	26.4	26.2	24.3	23.7
CPAP	5.1	5.8	11.5	12.3	12.5	12.6	12.6	12.5	12.1	11.9
Pacemaker	5.3	5.7	2.6	2.6	1.9	1.4	1	1	0.5	0.5
Complications										
Congestive heart failure during hospital stay	32.7	51.2	46.3	54.5	52.8	57.2	54.7	56.7	55.9	59.1
LVEF>50%	35.0	20.4	27.5	21.4	24.2	23.1	28.8	25.2	23.1	18.2
LVEF 41–50%	28.6	26.4	29.0	27.5	27.9	29.2	27.2	27.9	26.9	25.8
LVEF 31–40%	23.3	25.4	25.8	26.6	28.6	22.8	23.3	27.7	21.3	23.5
LVEF≤30%	13.2	27.9	17.7	24.6	19.3	25.0	20.7	19.2	28.7	32.5

Table 3 (continued)

	Quintile 1 *digoxin at discharge*		**Quintile 2** *digoxin at discharge*		**Quintile 3** *digoxin at discharge*		**Quintile 4** *digoxin at discharge*		**Quintile 5** *digoxin at discharge*	
	No (n=10,604)	Yes (n=1,557)	No (n=9,695)	Yes (n=2,467)	No (n=9,092)	Yes (n=3,054)	No (n=8,208)	Yes (n=3,942)	No (n=6,738)	Yes (n=5,406)
Procedures during hospital stay										
Coronary angiography	17.5	13.0	12.4	10.2	9.2	5.9	7.0	6.5	5.4	5.4
PTCA	8.7	6.2	5.1	4.6	3.4	2.1	2.6	2.3	1.8	1.8
CABG	2.3	2.3	2.2	1.7	1.3	1.3	1.1	1.0	0.9	0.9
Therapy at discharge										
ASA/platelet inhibitor	61.7	55.4	69.8	63.1	69.4	64.2	61.6	57.9	46.3	41.2
Beta-blocker	75.9	74.2	79.6	72.8	76.3	69.5	65.9	60.8	49.4	41.5
ACE inhibitor	40.5	50.5	49.3	51.8	53.4	53.6	54.2	54.4	61.0	64.7
Diuretic	32.8	51.6	58.3	66.1	72.2	76.3	82.2	84.8	90.5	94.7
Lipid-lowering drug	40.9	36.2	32.9	26.9	24.7	19.0	21.2	18.8	16.5	13.6
Long-acting nitrate	25.3	27.7	38.3	38.1	43.8	44.2	43.7	44.1	44.8	45.7
Anticoagulant therapy	13.7	34.7	15.4	25.6	15.0	22.6	21.5	28.3	38.4	46.4

Only patients with complete information on all variables were included. Values are percentages of patients unless otherwise stated

ACE angiotensin-converting enzyme, *CPAP* continuous positive airway pressure, *LVEF* left ventricular ejection fraction, *PTCA* percutaneous transluminal coronary angioplasty, *CABG* coronary artery bypass grafting, *ASA* acetylsalicylic acid, *ECG* electrocardiography.

* 25th, 50th and 75th percentiles

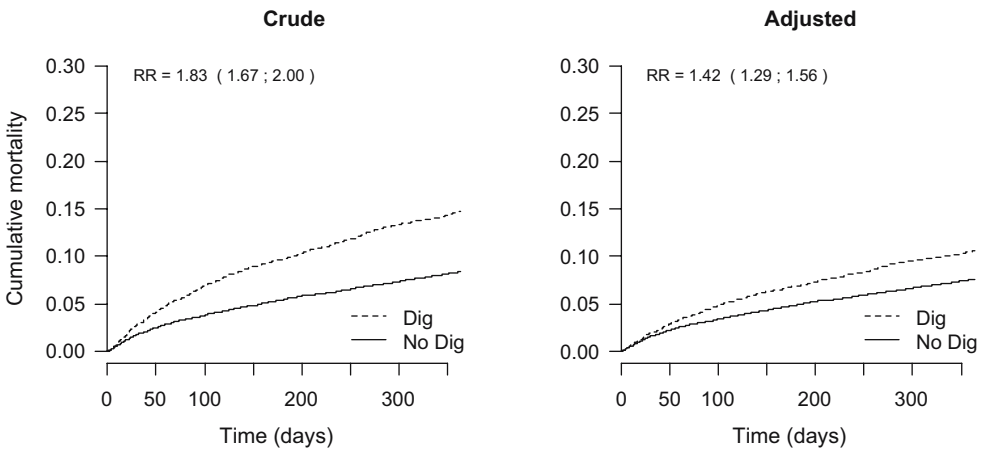

Fig. 2 One-year estimated cumulative mortality—atrial fibrillation. Estimated cumulative mortality in patients discharged with (*dashed line*) and without (*solid line*) digoxin. The *left figure* shows the crude cumulative mortality, and the *right* shows the cumulative mortality adjusted for propensity score and other discharge treatments. *RR* relative risk (95% confidence interval)

0.91–1.66), 1.22 (95% CI 0.94–1.58), and 0.98 (95% CI 0.83–1.16), respectively, after adjustment.

Effect of acute myocardial infarction

In patients with and without AMI, the RRs for death were 1.17 (95% CI 1.10–1.24) (4,743 received digoxin, 15,453 did not receive digoxin), and 1.10 (95% CI 1.04–1.16) (11,654 received digoxin, 28,817 did not receive digoxin), respectively, after adjustment.

Stratification by propensity score quintiles

The RR for death according to whether or not patients received digoxin stratified by propensity score quintile is shown in Table 4. There was a significant interaction between propensity score quintile and digoxin treatment in the AF and CHF groups so that lower quintiles were associated with higher RRs for death.

Discussion

This study showed that 23% of all patients in coronary care units in Sweden with AF without CHF were discharged with digoxin. At the same time, the adjusted overall RR for death was found to be 1.42 (95% CI 1.29–1.56) in these patients compared with those who did not receive the drug. On the other hand, digoxin therapy did not alter the overall mortality in patients with CHF, a finding in agreement with the results of the DIG trial [1]. Although there was a statistically significant difference in patients with CHF without AF, it was small and of doubtful relevance, albeit stratification by propensity score quintile suggests that digoxin could have a detrimental effect in those with the lowest baseline cardiac risk. The observed increase in mortality among patients with AF in this study was thus identical to that seen in the AFFIRM trial (RR=1.42) [5]. In that study, digoxin was found en passant to be the sole rate-control drug that was significantly related to survival: it increased the death rate. It was suggested that rather than reflecting a deleterious effect of digoxin on survival, the result might have been explainable by prescription of digoxin for patients at greater risk of death, such as those with CHF [5]. The results of our study indicate, however, that the latter theory is unlikely and instead suggest that digoxin is an independent risk factor for death among patients with AF without CHF on long-term therapy with this drug.

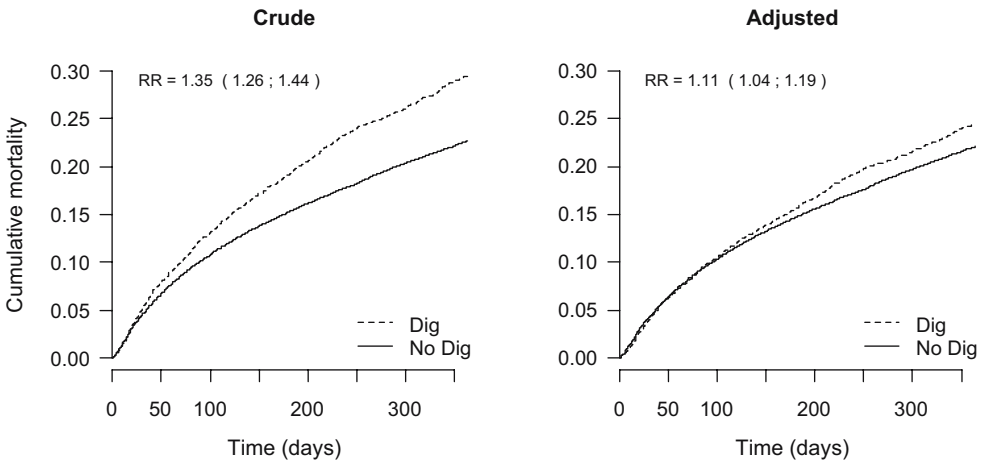

Fig. 3 One-year estimated cumulative mortality—congestive heart failure. Estimated cumulative mortality in patients discharged with (*dashed line*) and without (*solid line*) digoxin. The *left figure* shows the crude cumulative mortality, and the *right* shows the cumulative mortality adjusted for propensity score and other discharge treatments. *RR* relative risk (95% confidence interval)

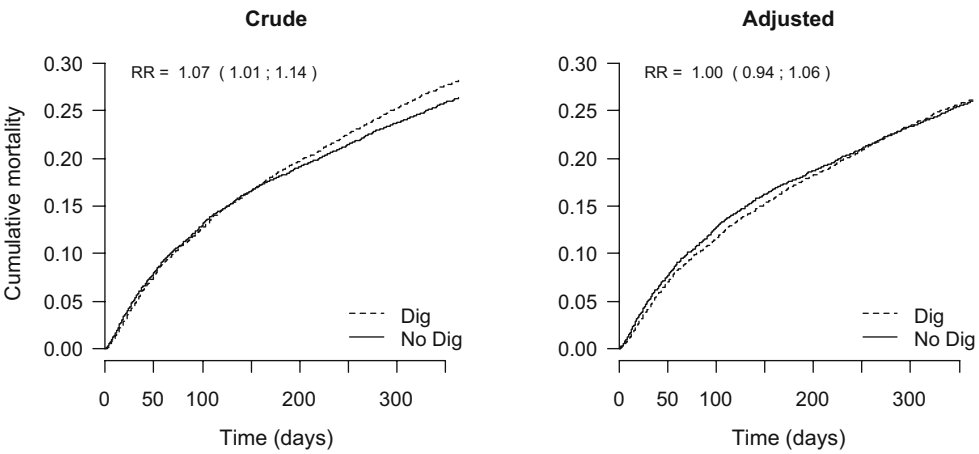

Fig. 4 One-year estimated cumulative mortality—atrial fibrillation + congestive heart failure. Estimated cumulative mortality in patients discharged with (*dashed line*) and without (*solid line*) digoxin. The *left figure* shows the crude cumulative mortality, and the *right* shows the cumulative mortality adjusted for propensity score and other discharge treatments. *RR* relative risk (95% confidence interval)

Why does the effect of digoxin on mortality differ between the groups? We cannot give a definite answer to that question, but a possible explanation may be that the combination of a positive inotropic and negative chronotropic effect of digoxin is beneficial, or at least not harmful, in patients with CHF, whereas it may be of more harm than benefit in those without CHF. Possible other effects may include baroreceptor function [39] and neuroendocrine activation [9]. For instance, the DIG trial showed that the digoxin effect of decreasing the hospitalization rate in CHF patients was more pronounced in patients with more severe CHF [1]. Furthermore, in that trial, no difference in total mortality was found between the digoxin-assigned and placebo-assigned groups, suggesting that the lower mortality from CHF deaths in the digoxin group could have been counterbalanced by an increase in deaths not due to CHF. Deaths from "other causes," presumed to be due to arrhythmias, were significantly higher in the digoxin (15%) than in the placebo group (13%) [29]. This leaves us with the question of whether patients without CHF, who thus would not benefit from the lower mortality from CHF, would only be exposed to a negative influence of digoxin on mortality. In this respect, the observed close correlation between a decreased LVEF and a decreased Na^+, K^+-ATPase concentration is interesting [21], suggesting that reduction of Na^+, K^+-ATPase in patients with CHF might serve compensatory purposes, with effects comparable to those of digoxin treatment. Although not the primary aim of the present study, it is interesting to note that the RRs for death in patients with AF and to some extent in patients with CHF was higher in the lowest propensity score quintiles, i.e., in those with the lowest baseline cardiac risk.

Although still widely used in clinical practice, perhaps on account of the theoretical advantage of its positive inotropic effect and its modifying effect on the ventricular rate and its obvious and beneficial short-term effects in the emergency setting, there is no evidence to suggest that digoxin has any effect on cardioversion in AF either in the presence or absence of CHF [2, 7, 12, 15] or any effect in suppressing recurrent AF [8]. During exercise and in patients with increased sympathetic activity, digoxin alone does not control the ventricular response unless large doses that are likely to produce intoxication are used [11, 17, 26]. Digoxin is generally not recommended as first-line therapy for management of AF, except in patients with concomitant CHF or left ventricular dysfunction [8]. In persistent AF, there are more effective alternatives, such as calcium channel blocking agents and beta-blockers [8], although digoxin is usually considered potentially useful as add-on therapy [16]. The present study did not address the effect of digoxin on mortality in the emergency setting, but the results cast doubts on the use of this drug for long-term treatment of AF in the absence of CHF.

A cohort study cannot be compared with a prospective randomized trial but it deserves to be pointed out that the strength of the present study includes the fact that it reflects the normal patient clientele, in that our patient cohort comprised unselected, consecutive patients, although strict

Table 4 Relative risk (RR) for death between patients discharged with vs. without digoxin among patients with atrial fibrillation (AF), congestive heart failure (CHF), and AF+CHF stratified by propensity score quintile

Propensity score quintile (1-year mortality prescribed digoxin, 1-year mortality not prescribed digoxin)	AF RR (95% CI)	CHF RR (95% CI)	AF+CHF RR (95% CI)
Q1 (6.6%, 11.9%)	2.28 (1.77, 2.95)	1.54 (1.14, 2.07)	0.92 (0.64, 1.33)
Q2 (15.0%, 19.4%)	1.70 (1.41, 2.06)	1.27 (1.05, 1.53)	1.04 (0.87, 1.25)
Q3 (20.9%, 23.4%)	1.28 (1.06, 1.54)	1.17 (1.01, 1.36)	1.06 (0.93, 1.22)
Q4 (25.1%, 25.5%)	1.24 (1.03, 1.47)	1.10 (0.96, 1.25)	0.92 (0.82, 1.03)
Q5 (28.7%, 30.3%)	0.98 (0.75, 1.29)	1.05 (0.94, 1.18)	1.04 (0.95, 1.14)

generalizability is limited to patients discharged from coronary care units. There were no exclusions due to presence or absence of specific risk factors or co-morbidities. The representativeness of the cohort was also strengthened by the fact that the patients were recruited from the general population at centres with different levels of care, including 73 of the 76 coronary care units within the whole of Sweden.

Limitations

Several limitations to this study need to be considered. First, the RIKS-HIA database does not include serum digoxin concentrations or digoxin doses. It may be argued that the higher observed mortality among patients with AF discharged with digoxin compared with those with CHF discharged with this drug could be due to a comparably higher dose in the former group. Subgroup analyses of the DIG trial have recently shown a relation between serum digoxin level and mortality [3, 24]. In men, the risk of death increased significantly with digoxin levels >1 ng/ml, whereas a digoxin level of 0.5 to 0.8 ng/ml was associated with a decrease in mortality [24]. Corresponding values in women were =1.2 ng/ml and 0.5 to 0.9 ng/ml, respectively [3]. Although we did not have information on the doses of digoxin given to the patients in our study, the findings in patients with concomitant AF and CHF, who were probably given a dose similar to that in patients with AF alone, argues against the possibility of a dose-related difference in mortality.

Second, although our results are based on a large cohort and have been adjusted for many confounding factors, a cohort study cannot compensate for all confounders and hence cannot replace a randomized controlled trial. Propensity analyses are inherently limited by the number and accuracy of the variables evaluated. Nevertheless, propensity scoring is a well-established tool that enables excellent matching of baseline characteristics [14], and moreover, there are limitations to randomized controlled trials also; for example, strict inclusion and exclusion criteria may limit the applicability of the study results to other, perhaps more typical, patient populations.

Third, for the majority of our patients the RIKS-HIA database did not include data on renal function or LVEF, two important determinants of mortality [10, 23]. However, among those patients for whom these variables were available, they did not affect the adjusted mortality estimates, indicating that our propensity score was satisfactory.

Fourth, we had no information about whether or not individual patients continued on digoxin therapy, or any other drug therapy, including combination therapy. It could be argued that patients who received digoxin at discharge were later switched to beta-blocker therapy. However, if this was the case, it would bias the results toward the null and cannot explain the findings in the AF group.

Fifth, data on antiarrhythmic therapy was not included in the analysis, as this variable was excluded from the RIKS-HIA database in 2004. At that time,antiarrhythmic therapy had been included as a general term, and an overall of 5% of the population had been on such treatment. With this low usage, other antiarrhythmic therapy, even if it differed extremely after adjustment between those who received digoxin and those who did not, is unlikely to explain the results.

Conclusion

Digoxin is widely used for treatment of AF and CHF, for short-term as well as long-term use. Among individuals aged 75 years and older, almost 20% were on medication with digoxin in 1996 [40]. Despite the declining use in the last few years, digoxin is still one of the most frequently prescribed drugs. It was listed twice among the top 200 prescriptions in 2000 [31]. This was also noted in our study. Our results indicate, however, that Swedish citizens admitted to coronary care units for AF without CHF and who are discharged with digoxin have an increased mortality compared with those not given the drug.

Ideally, these findings should be confirmed in prospective randomized controlled trials, but as such trials have no commercial interest, they are unlikely ever to be performed. In conclusion, the results of the present study indicate that digoxin is an independent risk factor for death among AF patients admitted to coronary care units and placed on long-term therapy with this drug, whereas there seems to be no excess risk in those with CHF.

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