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The impact of digoxin on mortality in patients with chronic systolic heart failure: A propensity-matched cohort study☆

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ABSTRACT

Background: Prior Studies showed mixed results in association of digoxin use with all-cause mortality (ACM). The aim of this analysis is to identify the impact of digoxin use on ACM in a contemporary heart failure (HF) cohort treated with guideline based therapy.

Methods: We included 2298 consecutive patients seen in an HF clinic between 2000 and 2015. Patients were considered to be a digoxin user if he/she received digoxin at any point during the enrollment period in the HF clinic. Patients were matched based on digoxin utility using propensity matching in 2–3:1 fashion. The primary outcome was ACM.

Result: Of 2298 patients, 325 digoxin users were matched with 750 non-digoxin users. The Matched cohort did not have differences among demographics and clinical variables except for worse HF symptomatology and increased prevalence of atrial fibrillation. Overall, the prevalence of the use of guideline suggested therapies was 96%. After a median follow-up duration of 4 years (IQR 2–6 years), digoxin use was associated with increased ACM (21.8% versus 12.9%, unadjusted HR = 1.81; 95% CI = 1.33 to 2.45; $p = 0.001$). This association remained significant after adjusting for the propensity score, atrial fibrillation, ejection fraction, and New York HF Class (HR = 1.74; 95% CI = 1.20 to 2.38; $p < 0.0001$).

Conclusion: In this analysis of well-treated HF patients, digoxin was associated with increased ACM. Further randomized controlled trials are needed to determine whether digoxin therapy should be used in well-treated HF patients. Until then, routine use of digoxin in clinical practice should be discouraged.

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1. Introduction

Heart failure (HF) is a major public health problem worldwide. It is the leading cause for hospitalizations in the western world, and it is associated with increased mortality and morbidity [1,2]. The current class I guidelines recommend potent therapies (angiotensin-converting enzymes inhibitors (ACEI), angiotensin II receptors antagonist (ARBs), beta-blockers (BB), and spironolactone and eplerenone) [3]. Digoxin, which is an inotrope, has been used for the treatment of symptomatic HF for many years [4,5]. Its use is mainly based on expert opinion and limited scientific evidence, which is limited to two withdrawal studies [6] and one large randomized placebo-controlled trial. The results of the DIG trial showed that digoxin did not improve all-cause mortality (p = 0.08). However, digoxin significantly reduced the number of hospitalizations for HF in this trial [4,7].

Recent evidence suggests contrary to these trials. The data started to emerge on the potential harmful effects of digoxin. A series of systematic reviews and meta-analysis have casted serious doubt on the benefit of digoxin when added to contemporary HF treatment [8]. In fact, some observations have indicated that digoxin may have a negative effect on survival [9–12]. However, the guideline based therapy use was not prevalent in these observational studies. There exists equipoise and

Abbreviations: HF, Heart failure; AF, Atrial fibrillation; CVDMP, Cardiovascular Disease Management Program; ACEI, Angiotensin-converting enzymes inhibitors; ARBs, Angiotensin II receptors antagonist; BB, Beta-blockers; CAD, Coronary artery disease; EMR, Electronic medical system; LV, Left ventricular.

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knowledge gap regarding use of digoxin in individuals treated with guideline based therapy and its association with mortality.

Therefore, the aim of this analysis is to determine the use of digoxin with all-cause mortality in a contemporary guideline based treated HF cohort.

2. Methods

2.1. Study design

This is a retrospective single center study that included all patients with the primary diagnosis of HF with low ejection fraction followed up in a nurse-Led Cardiovascular Disease Management Program (CVDMP) in King Abdulaziz Cardiac Centre (KACC) between 2000 and 2015. The detailed information about the CVDMP have been described before [13]. In short, the CVDMP in KACC was established in 2000, as a secondary prevention program that provides services for patients with history of HF, coronary artery diseases (CAD), diabetes mellitus, and prosthetic valves. Patients are followed up closely by high qualified nurse practitioners under the supervision of board certified cardiologist using predetermined algorithms. Since the program was established, dedicated well-designed databases were utilized in daily clinical activities such as patients' demographics, status on presentation and during follow-up, clinical assessment, frequent available laboratory investigations, and prescribed medications. These databases facilitated the assessment of efficacy of the clinic through monitoring the range of clinical indicators, the implementation of clinical guidelines, the compliance and observed medication side effect, and the monitoring of clinical outcomes.

2.2. Electronic medical record (EMR) and data collection

Patients' data were collected at the time of each patient's visit in the EMR reporting tool [13–15]. The variables are collected in real-time assessment of the clinical indictors via an easy to use web portal (Appendix Fig. 1) The data were regularly audited to identify missing information and data inconsistencies. This provided direct and timely feedback for the users and facilitated the availability of highly accurate data for research, scientific inquiry, and supported systematic improvement in care. The EMR database included patients' demographics, anthropometric measurements, vital signs, prior cardiac and non-cardiac history, history of HF (etiology, functional class, medications, relevant laboratory testing), cardiac procedures (cardiac catheterization, coronary percutaneous intervention, coronary artery bypass surgery), and non-invasive imaging assessments (echocardiography, nuclear imaging, cardiac computed tomography, or magnetic resonance imaging). This database was updated frequently in each visit according to recent changes in patient's medical condition. In addition, all utilized medications reviewed and adjusted per new changes in patient's status.

At the time of the analysis, all the variables were queried from the EMR database based on whether or not the patient met the inclusion and exclusion criteria. These variables were as follows: use of digoxin, ejection fraction, modifiable cardiovascular risk factors, prior cardiac history, and recent medications. The study was approved by ethical committee of our center (approval number RC16/001/R).

2.3. Inclusion and exclusion criteria

In this analysis, we included patients with HF and low ejection fraction (less than 45%). Patients were divided into two groups based on the use of digoxin. Patients were excluded if their vital status could not be verified or if they had HF with preserved left ventricular (LV) ejection fraction more than 45%.

2.4. Study definitions

A patient was considered to be a digoxin user if he/she received digoxin at any point during the enrollment period in the CVDMP clinic [13,15,16]. Prior coronary artery disease (CAD) was defined as prior diagnosis of myocardial infarction, coronary percutaneous intervention, coronary artery bypass surgery, or obstructive coronary artery disease on a prior angiogram. A prior diagnosis of systolic HF was defined as clinical diagnosis of systolic HF LV ejection fraction <45%. A diagnosis of obesity was made if the body mass index was more than 30 kg/m^2. Diabetes was defined as use of hypoglycemic medications, glycosylated hemoglobin more than 7%, or prior diagnosis of diabetes. Dyslipidemia was defined by use of lipid-lowering medications or prior diagnosis of a major lipid abnormality. Hypertension was defined as use of antihypertensive medications (ACEI, ARBs, BB, and diuretics) or a prior diagnosis of hypertension. The single blood pressure reading at the time of clinic visit was not used to diagnose hypertension. AF was defined as a prior diagnosis of at least paroxysmal or persistent AF at the time or if documented by electrocardiogram at the time of the clinic visit.

2.5. Outcomes

The primary outcome of the study was all-cause mortality. Patients were followed up closely using EMR databases. To account for events that may have occurred outside the EMR, patients who did not show up to the clinic within 6 months were called by the nurse practitioners to determine the vital status. If the patient or any member of his family could not be reached, the vital status was confirmed via the civil services records.

2.6. Statistical analyses

Patients were divided into 2 groups based on the use of digoxin. The two groups were compared using chi-square testing or Student's *t*-test as appropriate. To adjust for the influence of differences in the patients' baseline characteristics and comorbidities on survival, propensity score matching technique was used. A propensity score for each patient was generated using a logistic regression model predicting treatment with digoxin versus no treatment with digoxin on the demographic, clinical, and procedural characteristics given in Table 2. We matched patients on digoxin with no digoxin use by performing a 2–3:1 nearest neighbor match with a caliper width of 0.25 of the standard deviation of the logit of the propensity score [17,18]. One absolute SMD was used to determine success of the matching where values less than 10 and close to 0 indicated a good match [17,18]. The variables that did not match well were included in the Cox proportional hazard model. Analyses were performed using R statistical software and Match It package [19,20].

3. Results

3.1. Baseline characteristics

A total of 2298 patients were enrolled in the HF clinic (mean age 57.3 ± 12.7, 72% were male). The traditional cardiovascular risk factors were highly prevalent in this cohort: hypertension 64%, diabetes 74.6%, hyperlipidemia 74.2%, smoking 28.8%, and morbid obesity 36.2%. A total of 372 (16.2%) patients received digoxin for some time during their follow-up in the CVDMP clinic. Ischemic cardiomyopathy was prevalent in 52.2% of the patients. Table 1 shows the baseline clinical characteristics of the entire cohort stratified by digoxin use status. Patients who received digoxin were younger (mean age 57.8 ± 12 vs. 54.4 ± 14 years, $p < 0.001$) with no differences in gender ($p = 0.55$). Digoxin users had worse HF symptomatology as evident higher New York HF association functional class and higher prevalence of valvular heart disease and increased prevalence of atrial fibrillation. They were less likely to have coronary artery disease, diabetes mellitus, prior myocardial infarction, and hypertension.

3.2. Propensity matching

A propensity matching was performed 2–3:1 to account for the differences between the two groups. Postmatching, the average age was not different between the two groups (mean age 55.4 ± 13.4 vs. 54.7 ± 13.7 years, $p = 0.386$), males were 71% in the digoxin group vs. 70.4% among non-digoxin users. All comorbidities were well matched with no major residual differences between the two groups in comorbidities, past medical history (except for AF and NYHA Class), CAD family history, and evidence-based medication use (Table 2). The use of guideline-directed medical therapy is given in Table 3 and did not differ significantly among digoxin users and non-users.

3.3. Association of digoxin with all-cause mortality

After a median follow-up duration of 3.6 years (interquartile range 1.6–6.3 years), there were 168 deaths, 71/325 patients in the digoxin group (21.85%) compared to 97/750 death (12.93%) in the non-digoxin group. The Kaplan–Meier survival curves are shown in Fig. 1. Compared with non-digoxin users, digoxin use was associated with higher risk of mortality (unadjusted hazard ratio 1.81; 95% CI = 1.33 to 2.45; $p = 0.001$). This association of digoxin with all-cause mortality remained significant after adjusting for the propensity score and atrial fibrillation, ejection fraction, and NYHA class (HR = 1.74; 95% CI = 1.20 to 2.38; $p < 0.0001$). The mortality rates of mortality in digoxin users and non-users are shown in Fig. 2.

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