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Risk of digoxin intoxication in heart failure patients exposed to digoxin–diuretic interactions: a population-based study

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Increased frequency of electrolyte abnormalities and cardiac arrhythmias among patients exposed to digoxin–diuretic interactions has been well-documented in numerous descriptive studies.
- Nonetheless, a clear causal relationship has not been established in these studies.

WHAT THIS STUDY ADDS

- The risks of digoxin intoxication associated with use of digoxin in combination with any diuretic use, types of diuretics, combinations of diuretics, and individual diuretics were quantified using a population-based nested case–control study design.
- The combined therapy of digoxin with any diuretic is associated with a 3.08-fold increase in the risk of digoxin intoxication.
- Regarding diuretic class, the risk carried by loop diuretics is greater than that of thiazides or potassium–sparing diuretics, and the risk varies with different combinations of diuretic classes and individual diuretics.

AIMS

To quantify the digoxin intoxication risk associated with exposure to digoxin–diuretic interactions, and evaluate whether the risk varies by diuretic type, individually or in combination.

METHODS

This was a population-based nested case–control study in which data from the National Health Insurance Research Database (NHIRD) in Taiwan were analysed.

RESULTS

The study cohort comprised 154 058 heart failure (HF) patients taking digoxin between 2001 and 2004, in whom digoxin intoxication requiring a hospitalization (ICD-9 code 972.1) occurred in 595 cases. A total of 28 243 matched controls were also selected for analysis. Cases were 3.08 times (adjusted OR 3.08, 95% CI 2.50, 3.79) more likely to have been prescribed diuretic medication in the previous month than controls. Regarding the class of diuretics, loop diuretics carried the greatest risk (adjusted OR 2.97, 95% CI 2.35, 3.75), followed by thiazides (OR 2.36, 95% CI 1.70, 3.29) and potassium-sparing diuretics (OR 1.72, 95% CI 0.83, 3.56). The risk was also observed to vary with different combinations of diuretics, and the loops/thiazides/potassium-sparing diuretics combination carried the greatest risk (adjusted OR 6.85, 95% CI 4.93, 9.53). Among the individual diuretics examined, hydrochlorothiazide carried the greatest risk (adjusted OR 4.63, 95% CI 2.50, 8.57).

CONCLUSIONS

This study provided empirical evidence that digoxin–diuretic interactions increased the risk of hospitalization for digoxin intoxication in HF patients. The risk was particularly high for concomitant use of digoxin with a combination of loop diuretics, thiazide and potassium-sparing diuretics. The combined use of digoxin and diuretics should be avoided if possible.

Introduction

Interaction between digoxin and diuretics is one of the most common drug–drug interactions (DDI) experienced in the clinical setting [1, 2]. Diuretics are one of the most frequently prescribed drugs, given in the majority of heart failure (HF) cases [3], and are recommended for patients with symptomatic HF to control pulmonary congestion and peripheral oedema according to current treatment guidelines [4, 5]. Specifically, routine use of diuretics is suggested to improve greatly peripheral oedema and ventricular preload in cases of severe HF (stage C or D) according to the American College of Cardiology and the American Heart Association guidelines [4]. Regarding the use of digoxin in HF patients, this drug has multiple effects including enhanced cardiac contractility, improved baroreceptor function and decreased sympathetic tone [6], as well as reduced neurohormone concentrations [7]. Consequently, digoxin may relieve symptoms of congestion, control the heart rate in atrial fibrillation (AF), and improve ventricular function [8]. Though digoxin was not found to reduce the mortality rate, it may decrease the occurrence of hospitalization for worsening of HF [9] and reduce deteriorations in the clinical status of HF patients [10]. Currently, digoxin is a recommended treatment for i) patients with symptomatic HF and ii) HF patients with AF and a left ventricular ejection fraction (LVEF) of less than 40% [5]. Therefore, HF patients are much more likely to receive the combination therapy of digoxin and diuretics than other patients.

Three types of diuretics are primarily used for HF, each of which has a different therapeutic action [4, 5]. Loop diuretics are the treatment of choice for HF because of the substantial diuresis effect [11], and higher doses of loop diuretics are considered if the treatment response is insufficient [12]. In cases where patients receive a loop diuretic and diuretic resistance occurs, a switch to a different loop diuretic, the addition of a thiazide diuretic, or addition of spironolactone to the regimen is recommended [4, 5]. Thiazide diuretics, on the other hand, are not effective for HF when used alone, but are used in conjunction with loop diuretics to synergize the diuretic effect in patients with severe HF [13]. The third type of diuretic, potassium-sparing diuretics, are seldom used as sole agents for oedema; their main use is in combination with other diuretics to offset the effects of diuretics that increase potassium excretion [14]. Low-dose spironolactone is also used as an aldosterone antagonist to compensate for the activation of the renin-angiotensin-aldosterone system by other diuretics, and has been found to reduce the rate of mortality among patients with severe HF undergoing standard HF therapy [15]. Presently, spironolactone is considered an add-on to loop diuretic therapy if patients suffer hypokalaemia or diuretic resistance [4, 5]. Generally speaking, as the disease progresses, combinations of diuretics of different types are commonly prescribed to HF patients.

Although it is known that exposure to digoxin–diuretic interactions can lead to the development of serious cardiac arrhythmia, a clear cause–effect relationship has not been established [16]. Electrolyte disturbance is believed to be the main mechanism responsible for the digoxin–diuretic interactions [17, 18], and use of diuretics including thiazides and loop diuretics has been found to cause potassium or magnesium deficit [19–22]. However, these studies were limited by sample size, unavailability of detailed information on diuretics and lack of a control group.

More empirical evidence is therefore required. First, the actual risk of digoxin intoxication caused by interaction between digoxin and diuretics has not been quantified in a large HF population. Second, each of the three types of diuretic has a different therapeutic role and combinations of different types of diuretic are frequently used in the management of HF. It is therefore of great importance to evaluate whether the risk of digoxin intoxication varies by diuretic class or combination of diuretic types. Third, the effect of individual diuretics in combination with digoxin on the risk of digoxin intoxication has not been quantified. Without providing information regarding the risk involved in treatment with individual diuretics, it is difficult to weigh up the risks and benefits in order to select a diuretic to add to digoxin therapy for the treatment of HF patients.

This study aimed to evaluate the risk of digoxin intoxication associated with digoxin–diuretic interactions in a real world using a nested case–control study design. Specifically, the aim of this study was to quantify the risk of digoxin toxicity associated with co-prescriptions of digoxin and diuretics for varied uses, including different types of diuretics, different combinations of diuretic classes and individual diuretics in HF patients.

Methods

Data source

This study utilized data retrieved from the National Health Insurance Research Database (NHIRD) between 01/01/2000 and 31/12/2004, which contains all of the data regarding claims from Taiwan's National Health Insurance programme, a comprehensive and universal health insurance programme covering over 98% of the 23 million inhabitants of Taiwan. The National Health Research Institutes (NHRI) periodically receives the national health insurance claims from the Bureau of National Health Insurance, and then manages and constructs the claims to form the NHIRD. The NHIRD contains a record of every inpatient and outpatient medical claim as well as information on medications prescribed [23], and serves as an excellent data source for conducting population-based pharmacoepidemiology studies [24, 25]. The access and use of NHIRD for this study was approved by NHRI.

Cohort selection

We adopted a retrospective cohort design with a nested case–control analysis. The study cohort was first selected from the NHIRD during the 5 year study period. Patients were identified as suitable for inclusion if they received a diagnosis of HF based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes (428.xx, 398.91, 402.01, 402.11, 402.91, 404.00, 404.01, 404.03, 404.10, 404.11, 404.13, 404.90, 404.91, 404.93) in either an outpatient or inpatient service, and if they had started to take digoxin medication continuously. These ICD codes have been used for the identification of HF in other studies and have been validated elsewhere [26]. Patients were considered as having discontinued digoxin therapy if more than 3 months had elapsed between prescriptions. In addition, patients were excluded from the study if the date of the first prescription of digoxin preceded the date of first diagnosis of HF, or if the first digoxin prescription was received in the year 2000. Starting from the date of the first prescription of digoxin, the study cohort was followed-up until the occurrence of a hospital admission for digoxin intoxication, discontinuation of digoxin or the end of the study period, whichever came first.

Case definition and control selection

Case patients were identified as those with any inpatient diagnosis of digoxin intoxication (ICD-9 code 972.1). For patients with more than one incidence of hospitalization for digoxin intoxication, only the first hospitalization was considered for analysis. The index date was the date of hospital admission for digoxin intoxication in all analyses. Each case patient was matched with up to fifty controls nested within the study cohort by age (±5 years), gender, cohort entry date (±3 months), and occurrence of chronic kidney disease (ICD-9 code 585) before the index date, and controls were assigned the same index date as their corresponding case patient.

Exposure definition

Exposure to diuretics in the 1 month preceding the index date was assessed by several methods. First, use of diuretics was dichotomized: any use *vs.* no use. Second, the diuretics used were further divided into four categories: thiazides, loop diuretics, potassium-sparing diuretics and any combination of these three types. Third, combinations of diuretics were further categorized into combinations with loop diuretics, which included loop/thiazides, loop/thiazides/potassium-sparing, and loop/potassium-sparing combinations, and combinations without loop diuretics. Fourth, among a subset of cases and controls who received a single diuretic, the exposure to use of a single diuretic was measured. Fifth, as the sample size was sufficiently large, the individual use of furosemide was further quantified as the ratio of the average prescribed daily dose (PDD) to the defined daily dose (DDD) for investigation of the dose–response relationship. In order to examine the specificity of our findings, we evaluated whether there was an increased risk of digoxin toxicity associated with combination therapy of digoxin and any use of cephalexin, an antibiotic known not to potentiate the effects of digoxin.

Covariates

Comorbid diseases, concomitant medications, hospital characteristics and previous HF-related hospitalizations that could potentially influence the outcome were adjusted during multivariate analyses. The Charlson comorbidity index adapted by Deyo *et al.* [27, 28] and the occurrence of HF-related hospital admissions were measured during the year preceding the study cohort's entry date. The level and geographical area of the healthcare facilities attended by patients with HF and patients' related comorbid diseases including renal impairment (ICD-9 codes 580.9x, 581.9x, 583.4x, 583.6x, 583.7x, 584.xx, 586.xx), ventricular arrhythmias (ICD-9 codex 427.xx excluding 427.5x, 427.7x), myocardial ischaemia (ICD-9 codex 410.xx, 412.xx), hypothyroidism (ICD-9 codex 243.xx, 244.xx) and diabetes (ICD-9 code 250.xx) were measured in the 6 month period before the index date. These codes have been used previously to define the above mentioned diseases [29–32]. In addition, the dose of digoxin was measured as the ratio of PDD : DDD in the 3 months before the index date. Moreover, medications that might alter potassium concentrations were measured in the 1 month preceding the index date, including trimethoprim, angiotensin converting enzyme inhibitors (ACEIs), potassium supplements (potassium chloride, potassium citrate, potassium gluconate), medications that increase renal potassium loss (fludrocortisone, liquorice, carbenoxolone, aminoglycosides, cisplatin, amphotericin B), and those that cause transcellular potassium shift (theophylline, caffeine, β_2-adrenoceptor agonists) [33].

Statistical analysis

Conditional logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for quantifying the risk of hospitalization for digoxin intoxication. All confounders of interest were included in the model during multivariate analysis. Data cleaning was processed using SAS version 9.1 (SAS Institute, Cary, NC, USA), and the statistical analyses were conducted using STATA version 9.0 (STATA, College Station, TX, USA).

Sensitivity analysis

Several additional sensitivity analyses were conducted in order to assess the robustness of the main results. First, we excluded HF patients who had only received one digoxin prescription. Second, a different multivariate model selection process that involved inclusion of any remaining covariates that changed the ORs by more than 10% in the final model was adopted [34]. Third, we further adjusted for the

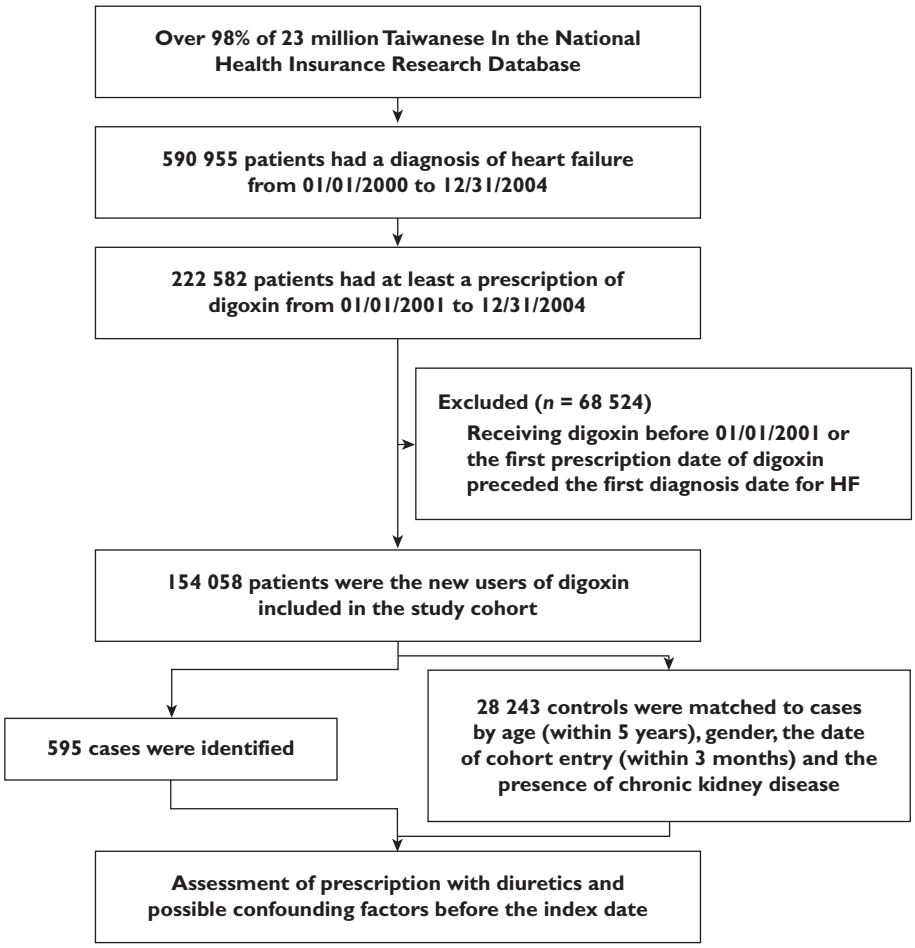

Figure 1
Study flow diagram

use of β-adrenoceptor blockers in the 1 month before the index date. Fourth, exposure to diuretics use was assessed over different time periods, including 1 week and 3 months before the index date.

Results

After applying the inclusion and exclusion criteria, the study cohort consisted of 154 058 HF patients who had begun digoxin therapy (Figure 1). The average age of the study cohort was 71 years, and the total follow-up time was 101 586 patient-years. We identified 595 patients as cases, of whom 89.1% were matched to 50 controls, and 10.9% were matched to fewer than 50 controls, giving a total of 28 243 matched controls. Table 1 shows the clinical and demographical characteristics of the cases and matched controls. Part of the baseline characteristics data of the cases has been reported elsewhere in an evaluation of the adverse clinical outcomes caused by a digoxin-clarithromycin interaction [35]. Cases and matched controls were comparable in the matching variables: mean age (77.1 *vs.* 77.1 years), gender (percentage of female, 67.9 *vs.* 68.1), presence of chronic kidney disease (37.8 *vs.* 36.1%), and median duration of digoxin use before the index date (83 *vs.* 90 days). Additionally, no major differences, defined as a more than 5% difference, were observed between the cases and controls in terms of the Charlson comorbidity index, the proportion of those diagnosed with renal impairment, myocardial ischaemia, hypothyroidism, or diabetes mellitus, the proportion of those receiving a prescription for trimethoprim, or the proportion of those being prescribed medications that increase renal potassium loss and cause transcellular potassium shift. Conversely, a greater proportion of cases had experienced previous hospitalization for HF (16.8 *vs.* 9.7%), had a diagnosis of ventricular arrhythmias (48.7 *vs.* 36.3%), received a prescription for potassium supplements (13.5 *vs.* 9.9%), and received a prescription for ACEIs (35.0 *vs.* 26.9%) in comparison with the controls. In addition, the median PDD : DDD ratio of digoxin in the cases was larger than that in the controls (0.8 *vs.* 0.5).

Table 1

Characteristics of cases and matched controls

	Cases (n = 595)	Controls (n = 28 243)
Age[a], mean (SD)	77.1 (12.2)	77.1 (10.3)
Days of using digoxin[a], median (IQR)	83 (26–356)	90 (45–313)
Female[a], *n* (%)	404 (67.9)	19 233 (68.1)
Chronic kidney disease[a], *n* (%)	225 (37.8)	10 192 (36.1)
Presence of HF related hospital admissions in previous year[b], *n* (%)	100 (16.8)	2 737 (9.7)
Doses of digoxin, PDD : DDD[c], median (IQR)	0.8 (0.6–1)	0.5 (0.5–0.7)
Charlson score[d], *n* (%)		
0	82 (13.8)	3 548 (12.6)
1	149 (25.0)	6 338 (22.4)
2	134 (22.5)	6 531 (23.1)
3	114 (19.2)	5 335 (18.9)
4	61 (10.3)	3 429 (12.1)
≥5	55 (9.2)	3 062 (10.9)
Healthcare facilities, *n* (%)		
Academic medical centres	167 (28.1)	6 913 (24.5)
Metropolitan hospitals	240 (40.0)	8 650 (30.6)
Local community hospitals	150 (25.2)	8 705 (30.8)
Physician clinics	38 (6.4)	3 975 (14.1)
Geographical area, *n* (%)		
Northern	270 (45.4)	11 995 (42.5)
Central	158 (26.6)	8 365 (29.6)
Southern	143 (24.0)	7 098 (25.1)
Eastern	24 (4.0)	785 (2.8)
Medical history, *n* (%)		
Renal impairment[e]	12 (2.0)	875 (3.1)
Ventricular arrhythmias[f]	290 (48.7)	10 259 (36.3)
Myocardial ischaemia[g]	43 (7.2)	1 678 (5.9)
Hypothyroidism[h]	4 (0.7)	199 (0.7)
Diabetes mellitus[i]	157 (26.4)	7 564 (26.8)
Medication history, *n* (%)		
Potassium supplements[j]	80 (13.5)	2 789 (9.9)
Trimethoprim	12 (2.0)	446 (1.6)
ACEIs[k]	208 (35.0)	7 594 (26.9)
Increased renal potassium loss[l]	51 (8.6)	2 526 (8.9)
Transcellular potassium shift[m]	141 (23.7)	7 123 (25.2)

[a]Matching variables. [b]Diagnosis of HF: ICD-9: 428.xx. [c]Average daily doses of digoxin were measured as the ratio of PDD : DDD. [d]Charlson comorbidity index adapted by Deyo *et al.* [28]. [e]Diagnosis of renal impairment: ICD-9: 580.9x, 581.9x, 583.4x, 583.6x, 583.7x, 584.xx, 586.xx. [f]Diagnosis of ventricular arrhythmias: ICD-9: 427.xx excluding 427.5x, 427.7x. [g]Diagnosis of myocardial ischaemia: ICD-9: 410.xx, 412.xx. [h]Diagnosis of hypothyroidism: ICD-9: 243.xx, 244.xx. [i]Diagnosis of diabetes mellitus: ICD-9: 250.0x-250.7x. [j]Potassium supplements comprised potassium chloride, potassium citrate, and potassium gluconate. [k]ACEIs included benazepril, captopril, cilazapril, enalapril, fosinopril, imidapril, lisinopril, perindopril, quinapril, ramipril. [l]Medications that increase renal potassium loss comprised fludrocortisone, licorice, carbenoxolone, aminoglycosides, cisplatin, amphotericin B. [m]Medications that shift transcellular potassium included theophylline, caffeine, β_2-adrenergic agonists. ACEIs, angiotensin-converting enzyme inhibitors; DDD, defined daily dose; HF, heart failure; IQR, interquartile range; PDD, prescribed daily dose.

Cases were found to be about 3.08 times (adjusted OR 3.08, 95% CI 2.50, 3.79) more likely to be prescribed any diuretic in the preceding 1 month in comparison with controls (Table 2). The risk varied by types of diuretics prescribed: for any combination of thiazides, loop diuretics and potassium-sparing diuretics, adjusted OR = 3.85, 95% CI 3.03, 4.90, for loop diuretics, adjusted OR = 2.97, 95% CI 2.35, 3.75, for thiazides, adjusted OR = 2.36, 95% CI = 1.70, 3.29 and for potassium-sparing diuretics, adjusted OR = 1.72, 95% CI 0.83, 3.56. Additionally, the ORs differed for various combinations with loop diuretics: the combination of loop/thiazides/potassium-sparing diuretics had the greatest OR (adjusted OR = 6.85, 95% CI 4.93, 9.53), followed by loop/thiazides (adjusted OR = 4.06, 95% CI 2.73, 6.05) and loop/potassium-sparing diuretics (adjusted OR = 3.79, 95% CI 2.75, 5.22). Furthermore, the use of cephalexin was not found to be associated with the risk of hospitalization for digoxin intoxication, which verified the specificity.

The main results were found through sensitivity analyses to be relatively robust. Restriction of the study cohort to patients who had received more than one digoxin prescription, adoption of the parsimonious models, or further adjustment for use of β-adrenoceptor blockers still achieved similar results to those of the main analysis: the point estimates of the ORs lay within the range of 90% to 110% that of the corresponding original ORs (data not shown). In addition, the association between risk of hospitalization for digoxin intoxication and various uses of diuretics still remained significant when diuretic use was assessed for different time periods before the index date (Table 2).

Table 3 presents the crude and adjusted ORs for the sole use of each individual diuretic measured in the 1 month preceding the index date. The results of multivariate analyses indicated that the sole use of hydrochlorothiazide, furosemide, trichlormethiazide or indapamide prior to the index date was associated with a 4.63-fold (95% CI 2.50, 8.57), 2.97-fold (95% CI 2.32, 3.80), 2.09-fold (95% CI 1.22, 3.57) and 2.08-fold (95% CI 1.13, 3.82) increase in the risk of hospitalization for digoxin toxicity, respectively, among HF patients treated with digoxin. Conversely, the sole use of bendroflumethiazide, bumetanide or spironolactone was not found to be statistically associated with increased risk of hospitalization.

The mean dose of furosemide within the study cohort, measured as the ratio of PDD : DDD, was 1.0, with a standard deviation of 1.2. There seemed to be a gradually increasing trend in the adjusted ORs across the four strata of doses of furosemide (Figure 2; ≤0.5 PDD : DDD 2.20; 0.5 to <1 PDD : DDD 2.99; 1 PDD : DDD 3.25; >1 PDD : DDD 3.31). Additionally, the OR increased by 13.3% (adjusted OR = 1.13, 95% CI 1.06, 1.21) per increment in the PDD : DDD ratio of furosemide.

Discussion

The overall results of this study suggest that combined use of digoxin with any diuretic(s) was significantly associated with a more than three-fold increase in the risk of hospitalization for digoxin intoxication. Regarding the class of diuretic prescribed, the risk was greatest for loop diuretics

Table 2

Risk of digoxin intoxication associated with diuretics use in patients receiving digoxin

	Case (n = 595)	Control (n = 28 243)	Univariate OR (95% CI)	Multivariate OR* (95% CI)
Diuretics prescribed in the 1 month preceding the index date				
Non-use, *n* (%)	127 (21.3)	13 070 (46.3)	1.00 (reference)	1.00 (reference)
Any use of diuretics, *n* (%)	468 (78.7)	15 173 (53.7)	3.23 (2.64, 3.94)	3.08 (2.50, 3.79)
Types of diuretics, *n* (%)				
Thiazides	52 (8.7)	2 270 (8.0)	2.40 (1.73, 3.32)	2.36 (1.70, 3.29)
Loop	209 (35.1)	7 104 (25.2)	3.09 (2.47, 3.86)	2.97 (2.35, 3.75)
Potassium-sparing	8 (1.3)	460 (1.6)	1.83 (0.89, 3.76)	1.72 (0.83, 3.56)
Any combinations	199 (33.5)	5 301 (18.8)	3.95 (3.15, 4.96)	3.85 (3.03, 4.90)
With loop†	165 (27.7)	3 875 (13.7)	4.55 (3.59, 5.78)	4.64 (3.60, 5.99)
Loop/thiazides	34 (5.7)	930 (3.3)	4.02 (2.73, 5.93)	4.06 (2.73, 6.05)
Loop/thiazides/potassium-sparing	65 (10.9)	1 035 (3.7)	6.73 (4.93, 9.19)	6.85 (4.93, 9.53)
Loop/potassium-sparing	64 (10.8)	1 642 (5.8)	4.14 (3.04, 5.63)	3.79 (2.75, 5.22)
Without loop	34 (5.7)	1 426 (5.1)	2.44 (1.66, 3.59)	2.51 (1.70, 3.70)
Diuretics prescribed in the 1 week preceding the index date				
Non-use, *n* (%)	386 (64.9)	23 905 (84.6)	1.00 (reference)	1.00 (reference)
Any use of diuretics, *n* (%)	209 (35.1)	4338 (15.4)	3.06 (2.57, 3.64)	2.88 (2.41, 3.45)
Types of diuretics, *n* (%)				
Thiazides	28 (4.7)	729 (2.6)	2.48 (1.67, 3.66)	2.48 (1.67, 3.69)
Loop	110 (18.5)	2 229 (7.9)	3.11 (2.50, 3.86)	2.92 (2.33, 3.65)
Potassium-sparing	7 (1.2)	178 (0.6)	2.44 (1.14, 5.25)	2.45 (1.13, 5.30)
Any combinations	64 (10.7)	1 194 (4.2)	3.44 (2.62, 4.52)	3.15 (2.38, 4.17)
With loop	46 (7.7)	766 (2.7)	3.86 (2.81, 5.30)	3.58 (2.59, 4.95)
Loop/thiazides	9 (1.5)	152 (0.5)	3.93 (1.99, 7.76)	3.61 (1.81, 7.20)
Loop/thiazides/potassium-sparing	16 (2.7)	137 (0.5)	7.55 (4.45, 12.82)	6.89 (4.00, 11.85)
Loop/potassium-sparing	21 (3.5)	437 (1.6)	3.03 (1.93, 4.76)	2.60 (1.64, 4.12)
Without loop	18 (3.0)	428 (1.5)	2.70 (1.67, 4.39)	2.64 (1.60, 4.34)
Diuretics prescribed in the 3 months preceding the index date				
Non-use, *n* (%)	77 (12.9)	6 982 (24.7)	1.00 (reference)	1.00 (reference)
Any use of diuretics, *n* (%)	518 (87.1)	21 261 (75.3)	2.32 (1.82, 2.96)	2.09 (1.63, 2.68)
Types of diuretics, *n* (%)				
Thiazides	42 (7.1)	2 438 (8.6)	1.62 (1.11, 2.36)	1.56 (1.06, 2.29)
Loop	200 (33.6)	8 592 (30.4)	2.24 (1.71, 2.94)	2.05 (1.56, 2.69)
Potassium-sparing	6 (1.0)	408 (1.4)	1.39 (0.60, 3.21)	1.32 (0.57, 3.06)
Any combinations	270 (45.4)	9 747 (34.5)	2.70 (2.08, 3.50)	2.40 (1.84, 3.14)
With loop	239 (40.2)	8 039 (28.5)	2.98 (2.28, 3.89)	2.67 (2.03, 3.53)
Loop/thiazides	57 (9.6)	2 094 (7.4)	2.79 (1.96, 3.97)	2.47 (1.73, 3.54)
Loop/thiazides/potassium-sparing	89 (15.0)	2 709 (9.6)	3.30 (2.40, 4.54)	2.91 (2.10, 4.02)
Loop/potassium-sparing	78 (13.1)	2 476 (8.8)	3.07 (2.22, 4.25)	2.60 (1.86, 3.62)
Without loop	31 (5.2)	1 708 (6.0)	1.67 (1.09, 2.55)	1.70 (1.11, 2.61)

*Multivariate analysis adjusted for presence of HF related hospital admissions, Charlson score, healthcare facilities, geographical area, ventricular arrhythmias, myocardial ischaemia, hypothyroidism, diabetes, potassium supplements, trimethoprim, ACEIs, increased renal potassium loss and transcellular potassium shift medication. †The use of combination of loops/osmotic diuretics was also observed; however, its ORs were unable to be provided because of very few exposed cases.

(adjusted OR 2.97, 95% CI 2.35, 3.75). Additionally, the observed risk also varied with different combinations of diuretic classes, and the combination of loops/thiazides/potassium-sparing diuretics carried the greatest risk (adjusted OR 6.85, 95% CI 4.93, 9.53). Furthermore, the risk of digoxin intoxication varied with the sole use of individual diuretics in combination with digoxin. Hydrochlorothiazide carried the highest risk of hospitalization for digoxin intoxication, followed by furosemide, trichlormethiazide and indapamide.

Regardless of the time period over which diuretic use was assessed, a significant association between risk of hospitalization for digoxin intoxication and the use of various diuretics in combination with digoxin existed. Of note, the level of risk observed when diuretic use was measured during the 1 week or 1 month prior to the index date was greater than that observed when diuretic use was assessed for the previous 3 months. Measurement of diuretic use during the 3 months before the index date might include a relatively larger proportion of HF patients with past use of diuretics, which might result in the difference in risk. Despite the variation in magnitude, the risk remained significant for all durations of diuretic use assessment preceding the index date.

Digoxin is still commonly used for the treatment of HF in Taiwan. Although the Digitalis Investigation Group Trial found that digoxin did not decrease the mortality rate in comparison with a placebo among HF patients with a LVEF $\leq$45% who were already taking diuretics and ACEIs [9], the use of digoxin was found to reduce the incidence of hospitalization for worsening HF [10] and decrease the HF-related treatment cost [36]. Digoxin is recommended

Table 3

Risk of digoxin intoxication associated with individual diuretic use

	Case (*n* = 383)	Control (*n* = 14 184)	Univariate OR (95% CI)	Multivariate OR* (95% CI)
Non-use, *n* (%)	124 (32.4)	8139 (57.4)	1.00 (reference)	1.00 (reference)
Diuretics, *n* (%)				
Thiazides				
Hydrochlorothiazide	13 (3.4)	202 (1.4)	4.28 (2.37, 7.71)	4.63 (2.50, 8.57)
Metolazone	4 (1.0)	80 (0.6)	3.27 (1.18, 9.10)	2.70 (0.96, 7.57)
Bendroflumethiazide	5 (1.3)	161 (1.1)	2.16 (0.87, 5.35)	1.75 (0.66, 4.67)
Indapamide	12 (3.1)	410 (2.9)	1.99 (1.09, 3.64)	2.08 (1.13, 3.82)
Trichlormethiazide	16 (4.2)	527 (3.7)	2.05 (1.21, 3.48)	2.09 (1.22, 3.57)
Loop diuretics				
Furosemide	196 (51.2)	4174 (29.4)	3.07 (2.44, 3.87)	2.97 (2.32, 3.80)
Bumetanide	5 (1.3)	156 (1.1)	2.14 (0.86, 5.30)	2.17 (0.87, 5.43)
Potassium-sparing				
Spironolactone	8 (2.1)	311 (2.2)	1.74 (0.84, 3.60)	1.67 (0.80, 3.48)

*Multivariate analysis adjusted for presence of HF related hospital admissions, Charlson score, healthcare facilities, geographical area, ventricular arrhythmias, myocardial ischaemia, hypothyroidism, diabetes, potassium supplements, trimethoprim, ACEIs, increased renal potassium loss and transcellular potassium shift medication.

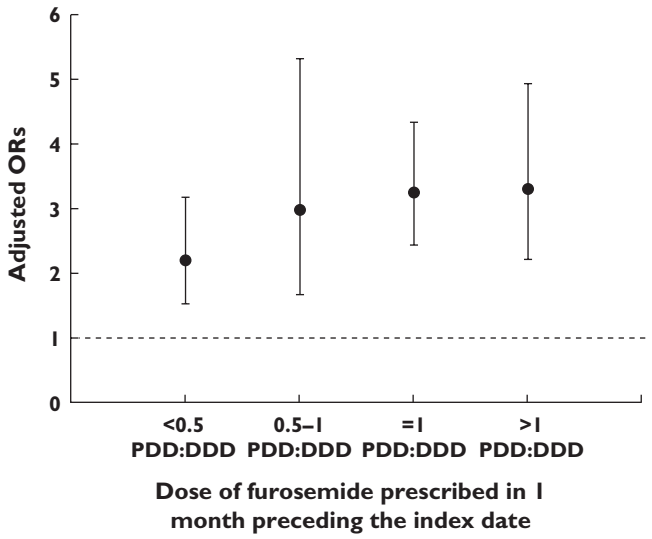

Figure 2

Risk of hospitalization for digoxin intoxication by doses of furosemide

for use in HF patients with AF according to current treatment guidelines [4, 5]. Our results also showed that 37.7% of all HF patients were being treated with digoxin during the study period. Therefore, as the proportion of HF patients receiving digoxin was not small, our findings deserve public notice, especially in countries in which digoxin is still frequently prescribed.

Adverse outcomes associated with the combined use of diuretics and digoxin have been reported previously [20–22], but the causal relationship was not established conclusively from these descriptive studies. Lim & Jacob assessed the serum and urine electrolyte concentrations of 10 HF patients receiving diuretics and digoxin, and found that five patients had magnesium deficiency, four of whom showed clinical symptoms of digoxin intoxication [21]. Other studies have also found that a high proportion of patients exposed to a digoxin–diuretic interaction had reduced serum potassium and/or magnesium concentrations, and an increased occurrence of cardiac arrhythmia has also been noted [20, 22, 37].

Changes in electrolyte concentrations, especially potassium, could be the main mechanism accounting for the adverse clinical outcomes caused by digoxin–diuretic interactions. Digoxin reversibly inhibits sodium-potassium ATPase (Na, K-ATPase or the Na, K pump) and thus inhibits sodium from being pumped out of cells and potassium from being pumped in [38]. In addition, potassium competes with digoxin with respect to binding to the Na, K pump. Therefore, as the serum potassium concentration is reduced by diuretics, the inhibition of the Na, K pump by digoxin is further facilitated [39]. Consequently, depletion of intracellular potassium might occur, which is associated with digoxin-induced arrhythmia [40]. Moreover, the potential sequelae of intracellular potassium depletion include hyponatraemia, hypochloraemia and hypochloraemic alkalosis.

Our results indicated that the risk of digoxin intoxication appeared to vary with the sole use of individual diuretics in combination with digoxin: for example, the adjusted OR for hydrochlorothiazide use (adjusted OR 4.63) is more than twice that of indapamide use (adjusted OR 2.08). Additionally, despite the stronger diuresis effect of furosemide in comparison with hydrochlorthiazide, the latter was found to carry a greater risk of digoxin intoxication than the former (adjusted ORs 4.63 *vs.* 2.97).

The observed differential effect of each individual diuretic on the risk of digoxin intoxication can probably be attributed to their differential ability to cause electrolyte abnormalities. Morgan & Davidson pointed out that the reduction in serum potassium concentration accompany-

ing a usual dose of hydrochlorothiazide was larger than that occurring with the usual dose of furosemide (0.6 mmol l^{-1} *vs.* 0.3 mmol l^{-1}) [17]. Their analyses also indicated that different thiazides could result in variation in the reduction of the serum potassium concentration. In addition, tubular secretion of digoxin is reduced when serum potassium concentrations are below 3 mmol l^{-1} [41]; i.e. hypokalaemia not only increases the serum digoxin concentration but also potentiates its toxicity [42]. Nonetheless, the hypomagnesia effect of individual diuretics has not been compared, and consequently, it is unclear whether the interplay between hypokalaemia and hypomagnesia can completely explain the observed differential effect of individual diuretics on the risk of digoxin intoxication.

The findings of the impact of different diuretic classes in combination with digoxin on the risk of digoxin intoxication might not be generalizable. We found that loop diuretics carried a greater risk than thiazides (adjusted ORs 2.97 *vs.* 2.36). However, the thiazide class of diuretics examined comprised several individual thiazides for which up to a two-fold difference in the adjusted ORs was observed. Additionally, the risk carried by furosemide was lower than that of hydrochlorothiazide by about 50%. Consequently, we observed that loop diuretics carried a greater risk of hospitalization for digoxin intoxication than thiazides.

According to the current treatment guidelines for HF [4, 5], certain combinations of diuretic types are recommended to improve diuretic responsiveness under certain circumstances. For example, it is suggested that thiazides be used in conjunction with loop diuretics in resistant HF patients in whom fluid retention is inadequately controlled [13]. In addition, spironolactone add-on to a loop diuretic is often considered useful for its potassium-sparing and antialdosterone effects, which reduce the incidence of adverse outcomes caused by loop diuretics [14]. Nonetheless, we found that any combination of diuretic types seemed to carry a greater risk of digoxin toxicity than the sole use of a diuretic of any class. Additionally, upon the addition of a potassium-sparing diuretic to the combination therapy of a loop diuretic and a thiazide, the risk was increased by 1.7 times (the adjusted OR increased from 4.06 to 6.85).

Potassium-sparing diuretics were found to inhibit renal elimination of digoxin [41, 43], which might partially explain why the add-on of potassium-sparing diuretics to other diuretics resulted in an increase in the risk. Specifically, spironolactone was found to inhibit tubular secretion of digoxin, and consequently led to an increase in the serum digoxin concentration [41]. It is possible, however, that potassium-sparing diuretics are added to the combined treatment of loop diuretics and thiazides in the possible presence of minor or subclinical digoxin intoxication. Regardless of the exact mechanisms involved, clinicians should still closely monitor HF patients being treated with digoxin when combination diuretic therapy is initiated and when potassium-sparing diuretics are added to other diuretics.

Our study has several unique attributes. The study cohort represents all HF patients who began to use digoxin in Taiwan during the study years. In other words, almost all HF patients on digoxin and diuretics have been captured in this analysis. Additionally, a large number of cases for digoxin intoxication were able to be evaluated using a nested case–control study design. Furthermore, to our knowledge, this is the first study to identify a risk of digoxin intoxication caused by exposure to diuretics among HF patients receiving digoxin. Moreover, in comparison with previous studies, this study identified a stronger cause–effect relationship, especially in the case of furosemide combined with digoxin, owing to the observed dose–response relationship. The validity of the present study was also strengthened by examining the specificity of our findings.

Some potential limitations of our study need to be emphasized. First, neither adherence to medications nor some possible confounding factors such as body weight and laboratory data on renal function were able to be obtained from the databases. Second, although several studies have adopted the use of ICD-9 codes obtained from the administrative records to identify patients with digoxin intoxication [44, 45], the coding accuracy for the relevant ICD-9 codes has not been evaluated. However, random miscoding is likely to underestimate an effect rather than overestimate the risk of interest. Third, the number of cases of digoxin intoxication was probably underestimated because only patients with digoxin intoxication requiring hospitalization were identified as cases. The use of hospitalization for digoxin intoxication as the outcome probably targets the severe clinical symptoms of digoxin intoxication such as arrhythmias. Fourth, this study might be subjected to a drug-channelling bias. For example, HF patients susceptible to digoxin intoxication might be treated with certain diuretic combinations. We did employ an individual matching scheme to select controls from the same cohort and used multivariate analyses to adjust for the available and important confounders such as dose of digoxin. Nonetheless, unmeasurable confounders such as HF severity might still exist. Fifth, not all of the individual diuretics were prescribed to cases and controls. Therefore, future study is warranted to investigate the effect of other individual diuretics in combination with digoxin on the risk of digoxin intoxication.

Overall, we found that any use of diuretics combined with digoxin increased the risk of hospitalization for digoxin intoxication, and the risk was higher for combinations of diuretic classes. In particular, the combination of loop diuretics, thiazides and potassium-sparing diuretics in conjunction with digoxin carried the highest risk. Clinicians should be vigilant in monitoring the presence of digoxin toxicity in HF patients treated with digoxin, especially when the complexity of the diuretic regimen is increased. In the meantime, other options for the management of HF

should be considered, and combination therapy of digoxin and diuretics should be avoided if possible.

Competing interests

There are no competing interests to declare.

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