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Original Research

Potentially inappropriate medications for patients with heart failure and risk of hospitalization from heart failure: A case-control study from Thailand

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Abstract

Background: Thailand have developed a list of potentially inappropriate medications for patients with heart failure (PIMHF). However, its association with clinical outcomes has not been evaluated in real-world clinical practice. **Objective:** To examine the association between the prescription of any PIMHF and hospitalization from heart failure (HF). **Methods**: A 1:1 matched case-control study was conducted. Data on HF patients visiting the study hospitals during 2017-2019 were obtained from the electronic medical record database. Patients with a history of first hospitalization due to HF and those with a history of outpatient department visits or non-HF hospitalization were defined as cases and controls, respectively. The association of hospitalization from HF with the prescription of any PIMHF was expressed as the adjusted odds ratio (aOR) and 95% confidence interval (95%CI), calculated using a conditional logistic regression (CLR) model. **Results:** After matching, 1,603 pairs of case and control were generated for the analysis. In total, 21 of 47 PIMHF were found to have been prescribed. Compared with the reference group of patients not prescribed any of the 21 PIMHF, those who had been prescribed a PIMHF had an aOR of 1.47 [95%CI 1.02:2.13]. NSAIDs/COX-2 inhibitors, oral short-acting beta-2 agonists, medications that promote fluid overload, and medications that elevate blood pressure were the four medication classes associated with the increased risk of hospitalization from HF (aOR = 2.64, [95%CI 1.30:5.38], aOR = 4.87, [95%CI 1.17:20.29], aOR = 1.50, [95%CI 1.01:2.22], and aOR = 2.51, [95%CI 1.26:4.99], respectively). **Conclusions:** The prescription of any of the 21 PIMHF found to have been prescribed in this study may increase the risk of hospitalization from HF. The Thai PIMHF list may be used in pharmacy practice as an assessment tool for the appropriate use of medication in HF patients.

INTRODUCTION

Heart failure (HF) is a major health problem affecting people worldwide. According to the American Heart Association (AHA) report, both the incidence and prevalence of HF in Americans remain high.[1] In Thailand, the morbidity and mortality rates for HF were 300 per 100,000 inpatients and 5.5% of patients hospitalized for HF, respectively.[2,3]

Despite recent advances in HF therapy, rehospitalization is still an adverse outcome frequently reported in HF patients. Multiple rehospitalizations are commonly found, with over half of HF patients rehospitalized within a year of hospital discharge.[4,5] In Thailand, rehospitalization rates within one and six months were reported to be 14.0% and 50.0%, respectively.[6,7] Rehospitalization leads directly to a high healthcare cost, which is estimated to reach up to $70 billion by 2030.[1]

Among the precipitating causes of hospitalization in HF patients, worsening HF was found to be the leading cause, accounting for 40.0-54.0% of all causes.[3,8,9] Several patient and clinical factors associated with the increased risk of HF hospitalization have been identified, e.g., age, sex, comorbidities, and laboratory findings.[10-14] Additionally, the use of certain medications that harmfully affect cardiac function can contribute to HF hospitalization.[15] According to the Thai ADHERE study, 1.7% of HF hospitalizations were induced by the use of new medications.[3]

HF patients commonly have both cardiovascular (CV) and non-CV comorbidities, requiring the prescription of multiple medications.[16-19] Polypharmacy (the use of ≥5 medications) is commonly reported in HF patients, with the median (interquartile range (IQR)) number of

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prescribed medications being up to 11 (8-17) items.[20,21] Importantly, the mean [standard deviation (SD)] number of non-CV medications was greater than that of HF medications (3.4 [2.7] vs. 2.1 [1.3]).[22] The use of multiple medications in HF patients who have other comorbidities can lead to a higher risk of drug-HF interactions.[17]

Drug-HF interactions are a safety concern in HF. Numerous medications can cause worsening HF, resulting in death or hospitalization. These medications are generally called potentially inappropriate medications for HF patients or PIMHF.[23,24] Previous studies have reported the use of PIMHF, e.g., calcium channel blockers, antiarrhythmics, alpha-blockers, oral corticosteroids, bronchodilators, psychotherapeutic drugs, and thiazolidinediones.[25,26] Using one HF-specific list of potentially inappropriate medications, the prevalence of PIMHF use was reported to be 14.6% of HF outpatients.[27]

Recently, the Thai PIMHF list has been created to use as an assessment tool to determine the appropriateness of prescribing medications in Thai HF patients.[28] However, the association of the Thai PIMHF list with clinical outcomes has not been evaluated in real-world clinical practice. Thus, this study aimed to evaluate the association of the prescription of any PIMHF from the Thai PIMHF list and hospitalization from HF.

MATERIALS AND METHODS

Study design and settings

A 1:1 matched case-control study was used. Two public hospitals, which serve as the academic and referral centers in the northern region of Thailand, were chosen as the study setting, including one tertiary care hospital (an 800-bed hospital) in Lampang Province and one secondary care hospital (a 231-bed hospital) in Phayao Province.

Patient and medical data were retrieved from the electronic medical record (EMR) database of each study setting. The EMR database comprises the following data: demographics, diagnosis codes (International Statistical Classification of Disease and Related Health Problems, 10th Revision, ICD-10), medication profiles, echocardiogram results, and laboratory findings. Data retrieval from the EMR database was performed by hospital staff who functioned as electronic database specialists.

The study protocol was reviewed and approved by the Institutional Review Board (IRB) of each study hospital (approval date: 18 November 2019 and protocol number: 84/62 for the tertiary care hospital, and approval date: 11 June 2019 and protocol number: 008/2562 for the secondary care hospital) prior to data retrieval.

Study subjects

All patients with a diagnosis of HF who had a history of hospital visits between 2017 and 2019 were retrieved from the EMR databases. Identification of HF patients was performed using ICD-10 codes related to HF diagnoses, including I09·9, I11·0, I13·0, I13·2, I25·5, I42·0, I42·5, I42·6, I42·7, I42·8, I42·9, I43, I43·0, I43·1, I43·2, I43·8, I50, I50·0, I50·1, I50·9, and P29·0.[29-31] The exclusion criteria included patients aged <18 years and patients diagnosed with rheumatic heart disease (I09.9), which was not considered relevant to HF by our cardiologists.

Study outcome

The primary outcome, which was used for defining cases, was hospitalization from HF occurring during a three-year period. The secondary outcome was in-hospital death or live discharge. The primary discharge diagnosis, which was presented with ICD-10 codes related to HF diagnoses, was used to identify hospitalization due to HF. The cause of death, which was recorded on the database, was used to identify in-hospital death from HF.

Cases and controls

The cases were the patients with a history of the primary outcome, including the patients discharged alive and the patients died in the hospital. The controls were the remaining patients with a history of outpatient department (OPD) visits or non-HF hospitalization.

One case was then matched with one control using the three matching variables, including sex, study settings, and index years. Sex was the most frequently identified factor associated with HF hospitalization.[11,13] Study settings (secondary or tertiary care hospital) and index years (2017, 2018, or 2019) were considered relevant to the standard of care, which might be different between the two study settings and between the three years of hospital visits, resulting in different rates of death or hospitalization and rates of PIMHF prescription.

Exposure group

The exposure group was defined as the patients prescribed any of the medication items from the Thai PIMHF list up to 1 year before the index date. Only the last prescription of each PIMHF was chosen for PIMHF detection.

The date of the event (i.e., date of admission or date of OPD visits) was assigned as the index date for each patient. The included patients had to have at least one prescription ahead of the index date to ensure that they had determinable drug exposure.

Procedures

All data available on the EMR database were retrospectively reviewed for one year before the index date. Study factors were characterized as patient factors, including sex, age on the index date, and whether they were elderly (age ≥60 years for Thais); clinical factors, including HF types classified by ejection fraction (EF, %), including HF with reduced EF (HF*r*EF, EF <40%), HF with mid-range EF (HF*mr*EF, EF 40-49%) and HF with preserved EF (HF*p*EF, EF ≥50%), comorbidities, and comorbidity

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score, calculated using the Charlson Comorbidity Index (CCI) score; laboratory findings; and medications prescribed both to inpatients and in the OPD.[29,32]

The study medications were specified using medication codes related to each HF medication and PIMHF. HF medications included the medication classes recommended for use by current guidelines.[33,34] The Thai PIMHF list was used to detect the exposure to PIMHF. Further details of the development process of the list are described in our previously published report.[28] Briefly, the list was developed and validated through literature reviews and a Delphi survey on consensus PIMHF among Thai HF experts. The Thai PIMHF list contains 47 medications that may cause worsening HF leading to hospitalization because they have a negative effect on cardiac function, such as elevated blood pressure or increased cardiac contractility and rate.[28] All listed medications are for all HF types, except for non-dihydropyridines calcium channel blockers (non-DHP CCBs), which are identified as PIMHF in patients with HF*r*EF. Sildenafil is identified as a PIMHF in concurrent nitrate users.[28] A one year period of exposure to PIMHF was chosen because it was considered the more appropriate marker of the study outcome than over a one year period.[24,27] To evaluate the association of class effects of PIMHF with the study outcome, PIMHF were classified according to therapeutic classes and the effect on cardiac function.

Statistical analysis

The sample size required for a 1:M matched case-control study was determined using Dupont's method.[35] The sample size required for the primary outcome was between 62 cases (for an adjusted odds ratio (aOR) = 3.05) and 1,701 cases (for an aOR = 1.26), using the following parameters: the probability of exposure among

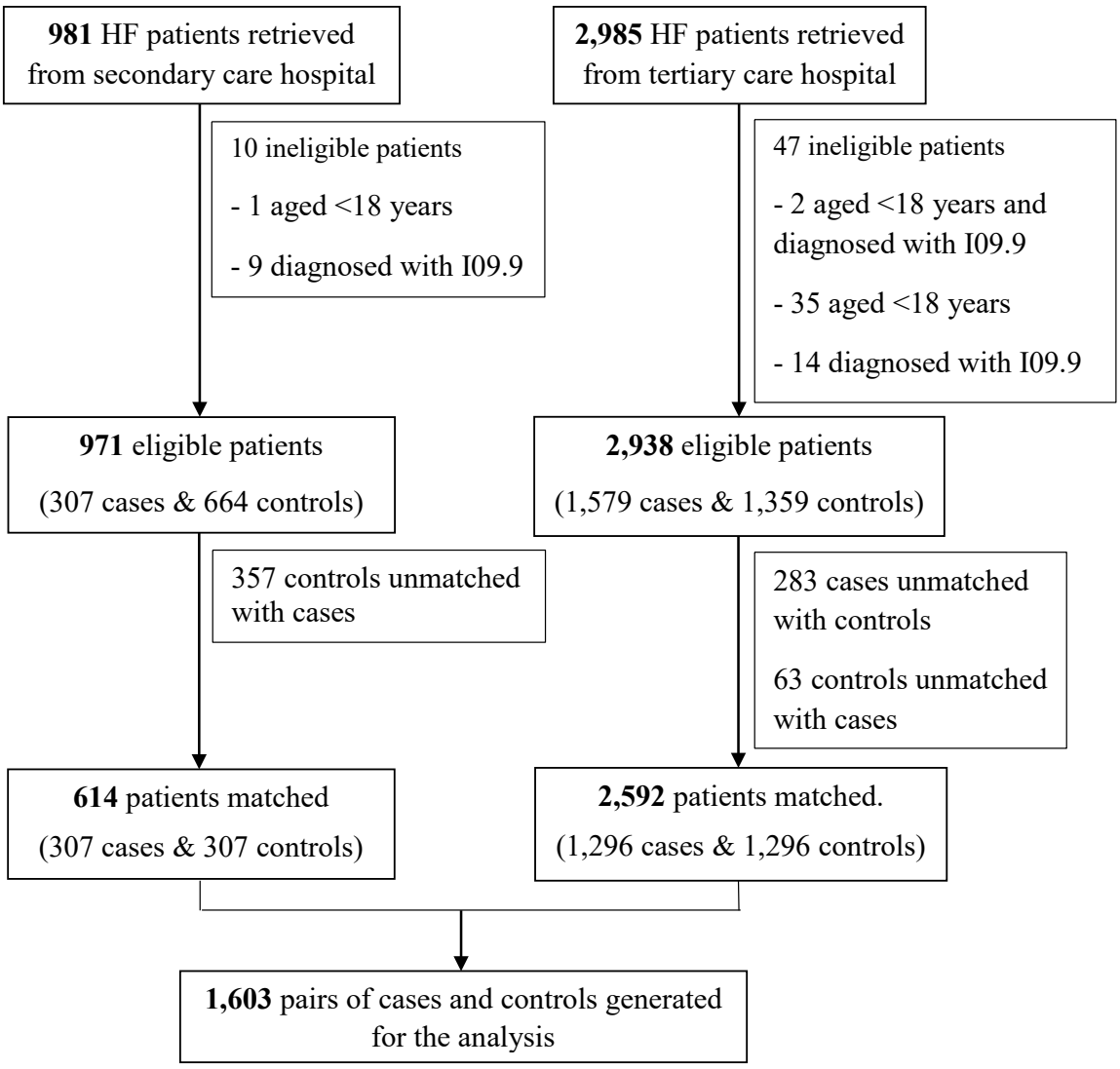

Figure 1. The recruitment process for cases and controls

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controls = 20%, the adjusted OR of HF events = 1.26 [95% confidence intervals (95%CI) 0.52:3.05], number of controls used for matching one case (M) = 1, and power of the analysis = 80%.[26, 27]Based on our findings, the probability of exposure among controls = 6.92%, the aOR of HF events = 1.47, and the number of cases included = 1,603, the power of the test was calculated as 85.3%.

The continuous variables with or without a normal distribution were analyzed and expressed as mean and SD or median and IQR (Q_1, Q_3), respectively. The categorical variables were analyzed and expressed as frequencies and percentages.

The strength of association between the prescription of any PIMHF and the study outcome was estimated using a conditional logistic regression (CLR) model and presented as crude and aOR and 95%CI.[36] In the univariate analysis, the study factors with *P*-value less than 0.05 were considered statistically significant and were then incorporated into the multivariate analysis. In the adjusted model, the variance inflation factor (VIF) was computed for each study factor to test if multicollinearity existed (the situation in which study factors in an adjusted model are highly correlated). The study factors with VIF ≥10 were excluded from the adjusted model.[37] A backward elimination procedure (where the most statistically insignificant variable is removed from each step until all remaining variables achieve a significance level of <0.05) was used for selection of the significant study factors.

All statistical analyses were performed with the use of Stata release 14.0 (Stata Corporation, College Station, Texas). All *P*-values were two-tailed.

RESULTS

Characteristics of study HF patients

The process of HF patient recruitment is shown in Figure 1. A total of 3,966 HF patients were initially retrieved from the two EMR databases. Fifty-seven patients were excluded due to ineligibility. Thus, the remaining patients (3,909) were included in the matching stage. After matching, a total of 1,603 pairs of cases and controls with the same sex, study settings, and index years were generated for the analysis. Of the 1,603 cases, 155 (9.67%) patients died of HF during hospitalization, and 1,448 patients were discharged alive.

The characteristics of all HF patients, and the patients classified as cases and controls are shown in Table 1. In total, more than half of the patients were male (50.97%). The average age was 65.38 (SD = 14.98) years, and over two-thirds were elderly patients (67.84%). HF*p*EF was most frequently found (49.38%), followed by HF*r*EF, and HF*mr*EF. Most patients (60.17%) had at least one CV comorbidity with the median (Q_1, Q_3) number of CV comorbidities equaling 1 (0, 2). Hypertension was the most frequently found, followed by renal failure, ischemic heart disease, and diabetes mellitus. For HF guideline-recommended medications, angiotensin converting enzyme inhibitors (ACEIs)/ angiotensin II receptor blockers (ARBs), beta-blockers, and aldosterone receptor antagonists (ARAs) were prescribed to approximately 18.22%, 10.73%, and 7.30%, respectively.

Prescription of PIMHF

Thirty nine of the 47 PIMHF was found to be available in the combined study hospitals (21 and 36 in the secondary and tertiary care hospitals, respectively). PIMHF prescribed to the study patients are summarized in Table 2. Only 21 available PIMHF were found to have been prescribed, with a proportion of 8.23%. The proportion of prescribed PIMHF was higher in cases than in the controls (9.54% vs. 6.92%). Prednisolone was the most often prescribed, followed by pioglitazone, naproxen, diclofenac, and salbutamol, respectively.

Association between prescription of PIMHF and the risk of the study outcome

Table 3 shows the study factors associated with the study outcome obtained from the univariate analysis. Prescription of the 21 PIMHF was found to be significantly associated with an increased risk of hospitalization from HF, with a crude OR of 1.47 [95%CI 1.12:1.92], *P*-value = 0.005. When adjusted for the other significant covariates, the association remained statistically significant (aOR = 1.47, [95%CI 1.02:2.13], *P*-value = 0.040), as shown in Table 4. No statistically significant association was observed between the prescription of the 21 PIMHF and either in-hospital death from HF or live discharge (Table 4). In a subgroup analysis, the prescription of the 21 PIMHF was significantly associated with the study outcome for the secondary care hospital (aOR = 1.66, [95%CI 1.06:2.61], *P*-value = 0.026), but not for the tertiary care hospital (aOR = 0.87, [95%CI 0.48-1.56], *P*-value = 0.644).

The association of the study outcome with the class effects of the PIMHF is shown in Table 5. Two therapeutic classes, NSAIDs/COX-2 inhibitors and oral short-acting beta-2 agonists (SABA), were significantly associated with an increased risk of hospitalization from HF (aOR = 2.64, [95%CI 1.30:5.38], *P*-value = 0.007 and aOR = 4.87, [95%CI 1.17:20.29], *P*-value = 0.029, respectively). Medications that promote fluid overload and medications that elevate blood pressure were the other two classes that were significantly associated with a higher risk of hospitalization from HF (aOR = 1.50, [95%CI 1.01:2.22], *P*-value = 0.041 and aOR = 2.51, [95%CI 1.26:4.99], *P*-value = 0.009, respectively).

DISCUSSION

The present study aimed to evaluate the association between the prescription of PIMHF, detected from the list of PIMHF recently developed in Thailand, and the risk of hospitalization from HF. Our findings showed that the prescription of any of the 21 PIMHF was significantly

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Table 1. The characteristics of all HF patients, cases (HF patients with study outcome), and controls (HF patients with no study outcome)

Characteristics	**Total patients n = 3,206**	**Controls n = 1,603**	**Cases n = 1,603**
Demographics			
Male sex	1,634 (50.97)	817 (50.97)	817 (50.97)
Age (years)	65.38 (SD = 14.98)	64.81 (SD = 14.93)	65.96 (SD = 15.01)
Age ≥60 years	2,175 (67.84)	1,062 (66.25)	1,113 (69.43)
Clinical characteristics			
HF*r*EF (EF <40%)	695 (32.94)	299 (30.08)	396 (35.48)
HF*mr*EF (EF 40-49%)	373 (17.68)	191 (19.22)	182 (16.31)
HF*p*EF (EF ≥50%)	1,042 (49.38)	504 (50.70)	538 (48.21)
Comorbidities	2,564 (79.98)	1,003 (62.57)	1,561 (97.38)
Number of comorbidities	3 (1, 4)	1 (0, 3)	4 (3, 5)
Cardiovascular (CV) comorbidities	1,929 (60.17)	619 (38.62)	1,310 (81.72)
Number of CV comorbidities	1 (0, 2)	0 (0, 1)	2 (1, 2)
Hypertension	1,101 (34.34)	316 (19.71)	785 (48.97)
Renal failure	622 (19.40)	171 (10.67)	451 (28.13)
Ischemic heart disease	572 (17.84)	140 (8.73)	432 (26.95)
Diabetes mellitus	565 (17.62)	135 (8.42)	430 (26.82)
Atrial fibrillation	562 (17.53)	140 (8.73)	422 (26.33)
Stroke	82 (2.56)	35 (2.18)	47 (2.93)
Dyslipidemia	80 (2.50)	69 (4.30)	11 (0.69)
Comorbidity score	1 (1, 2)	1 (1, 1)	2 (1, 3)
Comorbidity score ≥2	1,287 (40.14)	381 (23.77)	906 (56.52)
Laboratory findings			
Systolic blood pressure, SBP (mmHg)	129.90 (SD = 36.24)	129.13 (SD = 42.75)	130.71 (SD = 27.79)
Diastolic blood pressure, DBP (mmHg)	72.87 (SD = 17.67)	72.25 (SD = 16.73)	73.53 (SD = 18.61)
Heart rate, HR (b.p.m.)	85.98 (SD = 19.28)	84.25 (SD = 17.02)	87.80 (SD = 21.28)
Fasting blood sugar, FBS (mg/dL)	117.89 (SD = 50.91)	114.95 (SD = 45.41)	120.95 (SD = 55.93)
Hemoglobin A1C, HbA1C (mg%)	7.42 (SD = 2.10)	7.30 (SD = 2.00)	7.54 (SD = 2.19)
Ejection fraction, EF (%)	48.93 (SD = 17.40)	49.73 (SD = 16.90)	48.23 (SD = 17.81)
HF medications			
Diuretics	700 (21.83)	330 (20.59)	370 (23.08)
Calcium channel blockers (CCBs)	446 (13.91)	214 (13.35)	232 (14.47)
Angiotensin converting enzyme inhibitors (ACEIs)	363 (11.32)	178 (10.10)	185 (11.54)
Beta-blockers	344 (10.73)	165 (10.29)	179 (11.17)
Aldosterone receptor antagonists (ARAs)	234 (7.30)	107 (6.67)	127 (7.92)
Angiotensin II receptor blockers (ARBs)	221 (6.89)	110 (6.86)	111 (6.92)
Nitrates	210 (6.55)	102 (6.36)	108 (6.74)
Hydralazine	148 (4.62)	71 (4.43)	77 (4.80)
Digoxin	84 (2.62)	37 (2.31)	47 (2.93)
Ivabradine	3 (0.09)	1 (0.06)	2 (0.12)

All continuous variables are presented as mean (SD), except for number of comorbidities, number of CV comorbidities, and comorbidity score, which are presented as median and interquartile range (Q_1, Q_3).

Laboratory findings are the last measured values within a 6-month period before the index date.

SBP, DBP, HR, FBS, HbA1C, and EF are available for 972, 971, 968, 1,513, 627, and 2,110 patients, respectively.

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Table 2. A summary of the 21 prescribed PIMHF

PIMHF	Total patients (n = 3,206)	Controls (n = 1,603)	Cases (n = 1,603)
Prescribed any of the 21 PIMHF	264 (8.23)	111 (6.92)	153 (9.54)
The 21 prescribed PIMHF*			
prednisolone	91 (2.84)	35 (2.18)	56 (3.49)
pioglitazone	89 (2.78)	29 (1.81)	60 (3.74)
naproxen	37 (1.15)	18 (1.12)	19 (1.19)
diclofenac	27 (0.84)	12 (0.75)	15 (0.94)
salbutamol	18 (0.56)	7 (0.44)	11 (0.69)
ibuprofen	14 (0.44)	9 (0.56)	5 (0.31)
methotrexate	12 (0.37)	7 (0.44)	5 (0.31)
prazosin	9 (0.28)	6 (0.37)	3 (0.19)
pseudoephedrine	6 (0.19)	3 (0.19)	3 (0.19)
celecoxib	4 (0.12)	2 (0.12)	2 (0.12)
cyclophosphamide	4 (0.12)	2 (0.12)	2 (0.12)
ergotamine plus caffeine	3 (0.09)	2 (0.12)	1 (0.06)
clozapine	3 (0.09)	1 (0.06)	2 (0.12)
dexamethasone	2 (0.06)	1 (0.06)	1 (0.06)
melphalan	2 (0.06)	0 (0.00)	2 (0.12)
doxorubicin	2 (0.06)	2 (0.12)	0 (0.00)
paclitaxel	2 (0.06)	1 (0.06)	1 (0.06)
trastuzumab	2 (0.06)	2 (0.12)	0 (0.00)
verapamil (in HFrEF)	2 (0.06)	1 (0.06)	1 (0.06)
etoricoxib	2 (0.06)	1 (0.06)	1 (0.06)
fluorouracil	1 (0.03)	0 (0.00)	1 (0.06)

*Listed by frequency in descending order

Table 3. The univariate analysis

Study factors	Crude ORs [95%CIs]	*P*-values
Prescription of any of the 21 PIMHF	1.47 [1.12:1.92]	0.005*
Number of prescribed PIMHF	1.26 [1.04:1.53]	0.017*
Age (for every 10 year increase)	1.05 [1.01:1.10]	0.027*
Age ≥60 years	1.15 [0.99:1.34]	0.053
Comorbidity	20.24 [13.94:29.38]	<0.001*
Number of comorbidities	1.95 [1.83:2.07]	<0.001*
Cardiovascular (CV) comorbidity	6.80 [5.61:8.25]	<0.001*
Number of CV comorbidities	2.47 [2.25:2.71]	<0.001*
Hypertension	4.04 [3.39:4.82]	<0.001*
Renal failure	3.69 [2.97:4.58]	<0.001*
Diabetes mellitus	3.97 [3.19:4.96]	<0.001*
Atrial fibrillation	3.71 [2.98:4.60]	<0.001*
Ischemic heart disease	3.80 [3.06:4.72]	<0.001*
Stroke	1.36 [0.87:2.13]	0.176
Dyslipidemia	0.15 [0.08:0.30]	<0.001*
Comorbidity score ≥2	4.22 [3.55:5.00]	<0.001*
Comorbidity score	1.81 [1.67:1.97]	<0.001*
Systolic blood pressure, SBP	1.00 [0.99:1.01]	0.051
Diastolic blood pressure, DBP	1.00 [0.99:1.01]	0.291
Heart rate, HR (for every 10 b.p.m. increase)	1.10 [1.02:1.17]	0.007*
Fasting blood sugar, FBS	1.00 [0.99:1.05]	0.139
Hemoglobin A1C, HbA1C	1.13 [0.90:1.42]	0.271
Ejection fraction, EF	0.99 [0.98:1.00]	0.053
Diuretics	1.20 [0.99:1.45]	0.054
Calcium channel blockers (CCBs)	1.11 [0.89: 1.39]	0.315
Angiotensin converting enzyme inhibitors (ACEIs)	1.05 [0.82:1.34]	0.667
Beta blockers	1.09 [0.87:1.38]	0.416
Aldosterone receptor antagonists (ARAs)	1.20 [0.92:1.57]	0.174
Angiotensin II receptor blockers (ARBs)	1.00 [0.76:1.32]	0.945
Nitrates	1.06 [0.80:1.40]	0.668
Hydralazine	1.09 [0.78:1.52]	0.607
Digoxin	1.28 [0.82:1.99]	0.265

*Factor with *P*-value <0.05 were incorporated in an adjusted model.

associated with a 1.47-fold increased risk of hospitalization from HF ([95%CI 1.02:2.13], *P*-value = 0.040). Additionally, our study revealed that the following four medication classes were significantly associated with the increased risk of hospitalization from HF: NSAIDs/COX-2 inhibitors, oral SABA, medications that promote fluid overload, and medications that elevate blood pressure.

In this study, the association was evaluated using the framework of a case-control study because this study design enables us to evaluate the exposure to several PIMHF within the same period of time.[38] To ensure a true relationship between the exposure to PIMHF and the study outcome, biases inherent in a case-control study were considered and minimized in this study. For prevalence-incidence selection bias, only cases that received PIMHF before (1-365 days) the occurrence of the study outcome were selected, so a temporal relationship was explainable. For misclassification bias, cases and controls were classified using the cause of in-hospital death or the principal discharge diagnosis of hospitalization. Only eligible HF patients where the cause of in-hospital death or the principal discharge diagnosis of hospitalization were from HF were classified as cases, whereas the remaining were classified as controls. To avoid detection bias, PIMHF was detected by the use of hospital medication codes related to each PIMHF, so this could not be biased by either the patients or the investigators. For confounder bias, both matching technique and adjustment analysis were collectively used to minimize the influence of potential confounding factors.[39]

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Table 4.The multivariate analysis

Covariates	Adjusted ORs [95%CIs]	*P*-values
The primary outcome		
Prescription of any of the 21 PIMHF*	1.47 [1.02:2.13]	0.040
Age	0.989 [0.983:0.995]	<0.001
Hypertension	2.89 [2.31:3.61]	<0.001
Renal failure	2.21 [1.63:2.99]	<0.001
Diabetes mellitus	1.45 [1.05:2.00]	0.021
Atrial fibrillation	4.85 [3.72:6.32]	<0.001
Ischemic heart diseases	2.94 [2.25:3.85]	<0.001
Dyslipidemia	0.07 [0.03:0.16]	<0.001
Comorbidity score ≥2	1.86 [1.43:2.41]	<0.001
The secondary outcome		
In-hospital death from HF		
Prescription of any of the 21 PIMHF*	2.96 [0.86:10.23]	0.085
Live discharge		
Prescription of any of the 21 PIMHF*	1.38 [0.93:2.04]	0.108

*After adjusting for all the covariates (shown in Table 4) in the final model, yielding pseudo R^2 = 0.3592 and mean VIF = 1.80.
The number of observations for in-hospital deaths from HF and live discharge is 155 and 1,448, respectively.

Table 5. The univariate and multivariate analysis for PIMHF classifications (n = 3,206)

Classifications of PIMHF	Number of patients (%)	Crude ORs [95%CIs], *P*-values	Adjusted ORs [95%CIs],*P*-values*
Therapeutic classes			
Oral corticosteroids	93 (2.90)	1.41 [0.89:2.24], 0.135	1.41 [0.76:2.59], 0.266
Thiazolidinediones	89 (2.78)	2.34 [1.44:3.82], 0.001	1.23 [0.61:2.49], 0.548
NSAIDs/COX-2 inhibitors	65 (2.03)	1.20 [0.70:2.04], 0.501	2.64 [1.30:5.38], 0.007
Cancer drugs	22 (0.69)	0.75 [0.31:1.77], 0.514	0.94 [0.32:2.74], 0.918
Oral short-acting beta-2 agonists (SABA)	18 (0.56)	1.60 [0.52:4.89], 0.410	4.87 [1.17:20.29], 0.029
Effect on cardiac function			
Promotion of fluid overload	240 (7.49)	1.54 [1.16:2.04], 0.003	1.50 [1.01:2.22], 0.041
Elevation of blood pressure	72 (2.25)	1.30 [0.78:2.17], 0.303	2.51 [1.26:4.99], 0.009
Increase in cardiac contractility & rate	36 (1.12)	1.25 [0.58:2.67], 0.565	1.90 [0.68:5.27], 0.213
Cause of direct cardiotoxicity	27 (0.84)	0.78 [0.35:1.73], 0.549	1.09 [0.40:2.99], 0.858

*After adjusting for all the covariates (shown in Table 4) in the final model.
Reference group of the two classifications of PIMHF was the patients who received no PIMHF (n = 2,942).
For therapeutic classes, oral corticosteroids consist of dexamethasone and prednisolone; the thiazolidinedione was pioglitazone; NSAIDs/COX-2 inhibitors consist of diclofenac, ibuprofen, naproxen, celecoxib, and etoricoxib; cancer drugs consist of cyclophosphamide, doxorubicin, methotrexate, melphalan, paclitaxel, trastuzumab, and fluorouracil; the oral short-acting beta-2 agonist (SABA) was salbutamol.
For effect on cardiac function, the promotion of fluid overload consists of NSAIDs/COX-2 inhibitors, thiazolidinediones, oral corticosteroids, and prazosin; the elevation of blood pressure consists of NSAIDs/COX-2 inhibitors, pseudoephedrine, and ergotamine; the increase in cardiac contractility & rate consists of oral short-acting beta-2 agonists (SABA), pseudoephedrine, ergotamine, and prazosin; the cause of direct cardiotoxicity consists of cancer drugs clozapine, and ergotamine.

In our study, the rate of prescribing at least one PIMHF was only 8.23%, which seems smaller than the rate reported in Bermingham's study (14.60%).[27] However, the total number of patients receiving PIMHF was found to be more in our study than in the study by Bermingham, which could be due to the difference in the number of PIMHF contained in each list (47 items for the Thai list and 11 medications or medication classes for the St Vincent's list), consequently leading to a higher chance of finding patients receiving PIMHF in our study.[27, 28] With regard to the PIMHF found to have been prescribed in this study, oral corticosteroids (2.90%) were the most frequently prescribed, consistent with Bermingham's study, where it was reported that oral corticosteroids (17.5%) were one of the prescribed PIMHF.[27] The second most prescribed PIMHF was pioglitazone (one of the thiazolidinediones), with a prescription rate of 2.78%. It is recommended that thiazolidinediones are avoided for the treatment of diabetes mellitus in HF patients, due to their association with the higher risk of HF hospitalization.[42] NSAIDs/COX-2 inhibitors were prescribed to 2.03% of the patients, whereas none of the patients received these medication classes in Bermingham's study.[27] In Bermingham's study, the most prescribed PIMHF were non-DHP CCBs (26.3%), whereas only two patients with HF*r*EF received verapamil in our study. It is likely that most of the study patients had a result of EF, and the prescription of non-DHP CCBs is avoided in HF*r*EF. It is noted that these figures were determined in the case-control study, so they are not the true prevalence.

In this study, only an event from HF was chosen as the study outcome, because this outcome has a closer relationship with PIMHF than an event from all causes. The Thai PIMHF list was constituted on the basis of drug-HF interactions. All 47 listed medications have negative pharmacological effects on cardiac functions, so they may worsen or exacerbate HF, consequently leading to hospitalization or death.[23,24,28] Although each PIMHF has a difference in the onset of the effect after drug administration, from immediate (within a week) to delayed (over a year), only the last prescription of each PIMHF, occurring at any time within a one year period before the index date, was evaluated due to data

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limitations.[24] We believe that this length of time was not too long to deduce the causal relationship between exposure to PIMHF and the study outcome.

Our findings were consistent with a similar study that evaluated the relationship of one HF-specific list of PIMs (which is called the St Vincent's list of PIMs) with its clinical outcomes.[27] Despite the power of the test being insufficient, the study showed a tendency towards the positive association between the use of any 11 PIM items and the secondary outcome of HF events (HR = 1.26, [95%CI 0.52:3.05]). A positive association was found to be statistically significant for the primary outcome, but not for the secondary outcome. This is due to the insufficient power of the test for the secondary outcome. Nevertheless, this analysis showed a tendency towards a positive association (aOR >1) for a secondary outcome. When considering PIMHF according to the medication classes, our results were consistent with one previous study suggesting that NSAIDs are an independent predictor of an all-cause readmission within a year (HR = 1.07, [95%CI 1.01:1.12]).[13] NSAIDs/COX-2 inhibitors have a negative effect on HF because they can increase blood pressure and promote sodium and fluid retention through a reduction of prostaglandin I2 (PGI_2) synthesis (PGI_2 excretes sodium and fluid in the kidney), resulting in a heavy workload on the heart.[23,28] One study reported that the unadjusted mortality rates for oral beta-2 agonist (B2A) users were significantly higher than non-B2A users (HR = 1.30, [95%CI 1.03:1.65], *P*-value = 0.028), even though this association became insignificant for the adjusted mortality rates (HR = 1.04, [95%CI 0.77:1.41], *P*-value = 0.028).[40] Nevertheless, several studies have shown that the use of B2A was associated with the risk of mortality and HF hospitalization.[41] SABA can cause worsening HF by increasing cardiac contractility and rate through beta-1 receptor stimulation.[23,28]

HF patients with IHD had an increased risk of hospitalization from HF compared to those with no IHD, which is consistent with a study by Kossovsky *et al.* where a previous myocardial revascularization was suggested as a predictor of HF-related readmission.[10] The higher the patient's CCI score, the higher the risk of hospitalization from HF, which is consistent with the study by Arora.[11]

There were several strengths in the present study. First, data on large HF populations were used, yielding a sufficient power for the hypothesis test. Second, several of the HF-related ICD-10 codes were used for identifying HF patients. As suggested from literature reviews and confirmed by cardiologists, we can ensure the accuracy of the ICD-10 codes that we used. Finally, the odds ratio estimates were performed using an adjustment analysis that included several potential covariates.

There were some limitations in the study. First, only 21 prescribed PIMHF were evaluated, so the association of the remaining 26 PIMHF with the study outcome is still inconclusive. Nevertheless, it is still recommended that all 47 medications on the list are avoided as they can induce or cause worsening HF. Second, data determining the severity of HF (e.g., BNP or NYHA) were not routinely collected, so the difference in HF severity between cases and controls, which could be related to both the prescription of PIMHF and the study outcome, was lacking. Third, data on the amount and duration of exposure to PIMHF were lacking, so the dose-response and continuity of PIMHF use could not be assessed. Fourth, the rate of PIMHF use might be higher than this, because the patients might receive PIMHF from other sources. Fifth, the proportion of patients admitted to other hospitals was unknown. Finally, our findings might not be generalized to other health facilities where the availability of PIMHF and the patterns of drug prescribing are different.

In conclusion, the increased risk of hospitalization from HF is likely to be associated with the prescription of the 21 PIMHF from the Thai PIMHF list. To prevent HF patients from such a risk, the Thai PIMHF list may be used as an assessment tool to determine the appropriateness of medication use in HF patients in general pharmacy practice.

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CONFLICTS OF INTEREST

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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