Background: Several medications may worsen heart failure (HF), and they are considered as potentially inappropriate medications for patients with heart failure (PIMHF). No studies have reported the prevalence of PIMHF use and its associated factors in Thai HF patients.

Objective: To determine the prevalence of PIMHF use and identify the factors associated with PIMHF use.

Materials and Methods: A cross-sectional analytical study was conducted using data on HF patients obtained from the electronic medical databases (EMD) of two hospitals, including a secondary- and a tertiary-care hospital. Data collected included demographics, diagnoses, and medication items prescribed during 2016–2019. The prevalence of PIMHF use identified by the Thailand list of PIMHF was determined. Patient and clinical factors were examined for association with PIMHF use by calculating the adjusted odds ratio (aOR) and 95% confidence interval (95% CI) using a binary logistic regression analysis.

Results: From the EMD, 972 and 2,888 eligible HF patients from a secondary- and a tertiary-care hospital, respectively, were included in this study. The prevalence of PIMHF use was 45.16% and 33.07% at a secondary- and a tertiary-care hospital, respectively. The PIMHF distribution appeared similar between the two study hospitals, with oral corticosteroids being the most frequently prescribed, followed by NSAIDs, COX-2 inhibitors, and thiazolidinediones. The factors associated with PIMHF use were non-cardiovascular (non-CVD) co-morbidities, including diabetes mellitus (aOR = 1.68, 95%CI = 1.42–1.99), chronic pulmonary diseases (aOR = 2.69, 95%CI = 2.07–3.48), connective tissue diseases (aOR = 7.16, 95%CI = 3.09–16.57), and cancer (aOR = 1.97, 95%CI = 1.20–3.22).

Conclusion: PIMHF use was prevalent in Thai HF patients and associated with certain non-CVD co-morbidities. A careful prescription and a review of medication use should focus on HF patients with specific non-CVD co-morbidities.

Keywords: Heart failure; Potentially inappropriate medications; Thailand criteria; Prevalence; Factors associated

What's already known about this topic?

- HF patients tend to have several co-morbidities, which may be cardiovascular (CVD) or non-cardiovascular (non-CVD), leading to a greater requirement of several medications.

- Heart failure-specific lists of potentially inappropriate medication have been developed, including Thailand.

What does this article add?

- The prevalence of PIMHF according to the Thailand list of PIMHF in real clinical practice has not been reported.

- The present study conducted using real clinical data on HF patients revealed the prevalence of PIMHF use and the non-CVD co-morbidities associated with PIMHF use.

Introduction

Heart failure (HF) is a chronic condition with a high prevalence and incidence.[1] In Thailand, rates of morbidity and in-hospital mortality in HF patients were reported to be 300/100,000 people[2] and 5.5%[3], respectively.

Hospitalization has been recognized as a frequent adverse outcome of caring for HF patients and has led to a high healthcare cost.[4, 5] Rates of all-cause hospitalization remain high.[6, 7] Over half of HF patients were re-hospitalized within 1 year, and multiple re-hospitalizations were found to be common.[8, 9] Hospitalization had a direct effect on a healthcare cost, which were estimated to be $70 billion in 2030.[1]

Worsening HF was reported to be the major cause of hospitalization[4], accounting for 16.5%[8] to 37.0%[10] of all causes. It is caused by exposure to precipitating factors.[11] Despite several precipitating factors, medication use, including nonadherence to HF medications and use of certain medications that adversely affect cardiac function, were reported and considered preventable factors.[3, 11]

HF patients tend to have multiple co-morbidities, which may be cardiovascular (CVD) or non-cardiovascular (non-CVD). A European survey revealed that three-fourths of HF patients had 1 co-morbidity.[12] Several non-CVD co-morbidities in HF patients were reported, e.g., diabetes, COPD, cancer etc.[13] Multiple co-morbidities led to a greater requirement for the prescription of multiple medications, including medications for HF and for co-morbidities.[14-19] A previous study reported that the mean number of medications prescribed to HF patients rose from 6.8 in 1998–1999 to 7.5 in 2000–2001. Furthermore, the increase in the number of medications was greater for non-CVD drugs than for CVD drugs (19% vs 8%).[20] Thus, medication use has become a particular concern in caring for HF patients having co-morbidities because it can lead to drug-related problems, especially drug-disease interactions.[15]

Mis-prescribing (i.e., drug-HF interaction) has been an under-recognized problem in treating HF patients with co-morbidities. Several medications have harmful effects on cardiac structure or function.[19, 21] Those medications are considered as potentially inappropriate medications for patients with HF (PIMHF). Some PIMHF were reported to be prescribed to HF patients with specific co-morbidities, e.g., thiazolidinediones for diabetes, NSAIDs or COX-2 inhibitors for rheumatoid arthritis, β_2-agonists for COPD, and trastuzumab or doxorubicin for breast cancer.[13, 20] Also, a recent study revealed that the prevalence of PIMHF use identified by an HF-specific list of PIM was 14.6% among HF outpatients.[22]

Recently, a list of PIMHF has been developed in Thailand.[23] This explicit set of criteria contains 47 consensual PIMHF items considered relevant to Thai HF patients. PIMHF use in Thai HF patients in real clinical practice is unknown. The present study was carried out to evaluate the prevalence of PIMHF use identified by the Thailand list of PIMHF and to identify the factors associated with PIMHF use.

Materials and Methods

Study design and settings

A cross-sectional, analytical design was used. Data on patients with a diagnosis of HF were obtained from the electronic medical databases (EMD) of two hospitals, including a secondary-care hospital (a 231-bed public hospital) in Phayao Province and a tertiary-care hospital (a 743-bed public hospital) in Lampang Province. Both study hospitals serve as referral centers for the upper northern region of Thailand. The EMD comprises the following data: patient demographics, coding of principal and secondary diagnosis (ICD-10 code), and prescriptions at inpatient and outpatient departments. The study protocol was approved by the Research Ethics Committee of the study hospitals prior to data collection.

Subjects

Data on all patients diagnosed with HF who visited the study hospitals between January 1, 2016 and December 31, 2019 were retrieved from the EMD. Patients were identified as having HF using the following International Statistical Classification of Disease and Related Health Problems, 10th Revision (ICD-10) codes: 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.[24-26] After HF patients were identified, those with age <18 years and those with no history of prescription during 2016–2019 were excluded from the study.

Procedures

All independent variables of interest were obtained from the EMD. Independent variables were characterized as patient demographics, including sex and age (on December 31, 2015); clinical characteristics, including HF classification according to ejection fraction (EF), CVD co-morbidities, non-CVD co-morbidities, and the Charlson co-morbidity index (CCI) score.[27] The CCI score was calculated for each patient using coding algorithms to define relevant co-morbidities in ICD-10 administrative data.[24]; and HF medications recommended for use by HF guidelines.[28, 29]

All medication items of interest were identified using the medication codes of each study hospital. The Thailand list of PIMHF, an explicit criterion containing 47 PIMHF items and their effects on cardiac function[23], was used for PIMHF detection. A period of 4 years (2016–2019) was chosen to study the prevalence because PIMHF use was more likely to be detected in this period than at one time point. At the time of this study, 21 and 36 PIMHF items were found to be available at secondary- and tertiary-care hospitals, respectively. According to the Thailand list of PIMHF, diltiazem and verapamil were considered as PIMHF only when used in HFrEF (EF <40%). Sildenafil was considered as PIMHF only when used with nitrates. Thus, these conditions were checked to assess whether the use of these three medications was considered as PIMHF.

Statistical analysis

Continuous variables were analyzed and presented as mean ± standard deviation (s.d.) for normally distributed continuous variables or median and interquartile range (Q_1, Q_3) for non-normally distributed continuous variables. Categorical variables were analyzed and presented as frequencies and percentages. The prevalence of PIMHF use was calculated and presented as percentages for each study hospital.

Both study hospitals had no differences in CVD co-morbidities, non-CVD co-morbidities, and PIMHF distribution, so the data from both hospitals were pooled for an analysis of factor identification. To identify the factors associated with PIMHF use, a binary logistic regression model was used to estimate crude and adjusted odds ratios for each potential factor.

In a univariate analysis, factors with p-values < 0.05 were selected for a multicollinearity test. In a multicollinearity test, factors highly correlated with another factor and considered less clinically significant were excluded. In a multivariate analysis, a backward elimination method, in which the least significant variable was discarded at each step, was used until all remaining variables in the model reached a significance level of 0.05 or less. Analyses were performed using Stata release 14.0 (Stata Corporation, College Station, Texas). All p-values were two-tailed.

Results

Patient characteristics

From the EMD of study hospitals, 972 and 2,888 eligible HF patients from one secondary- and one tertiary-care hospital, respectively were included in the study (Figure 1).

Characteristics of the total patient group and the patients from each study hospital are shown in Table 1. Half of the patients (50.47%) were female, and the mean age was 63.62 ± 14.69 years. The majority (81.48%) had ≥1 co-morbidity, and the median number of co-morbidities was three (1, 4). In all, 41.37% of patients had ≥1 non-CVD co-morbidity: renal failure was the most frequently found, followed by diabetes mellitus, and chronic pulmonary diseases. Regarding HF medications, ACEI, ARB, and BB were prescribed to 43.86%, 42.28%, and 49.22% of the patients, respectively.

Prevalence of PIMHF use

Table 2 provides summary results for all PIMHF items prescribed at each study hospital. Fifteen of 21 and 29 of 36 available PIMHF items at a secondary- and a tertiary-care hospital, respectively were found to be prescribed to the study patients.

PIMHF items were prescribed to 45.16% and 33.07% of the patients at a secondary- and a tertiary-care hospital, respectively. The PIMHF distribution was found to be similar at both study hospitals. The most frequently prescribed PIMHF was oral corticosteroids, followed by NSAIDs and COX-2 inhibitors and pioglitazone. Cancer drugs were also found to be used in HF patients. Twelve of 21 patients treated with diltiazem had EF, and only two of them had HFrEF. Thirty-two of 40 patients treated with verapamil had EF, and only six of them had HFrEF. Thus, eight patients were considered to have received PIMHF.

Factors associated with PIMHF use

Table 3 shows the potential factors found to be associated with PIMHF use obtained from a univariate analysis. Patient factors and certain non-CVD co-morbidities were associated with a higher probability of PIMHF use.

In a multivariate analysis, non-CVD co-morbidities, including diabetes mellitus (DM), chronic pulmonary diseases (CPD), connective tissue diseases (CTD), and cancer, were found to be significantly associated with PIMHF use. Compared with the referent group of subjects who had no DM, those with DM had an odds ratio of 1.68 (95% CI = 1.42–1.99). Compared with the referent group of subjects who had no CPD, those with CPD had an odds ratio of 2.69 (95% CI = 2.07–3.48). Compared with the referent group of subjects who had no CTD, those with CTD had an odds ratio of 7.16 (95% CI = 3.09–16.57). Compared with the referent group of subjects who had no cancer, those with cancer had an odds ratio of 1.97 (95% CI = 1.20–3.22).

In a subgroup analysis, those non-CVD co-morbidities were positively associated with specific PIMHF use. DM was associated with pioglitazone (OR = 12.71, 95%CI = 9.53–16.96). CPD was associated with oral corticosteroids (OR = 6.14, 95%CI = 4.93–8.35) and with salbutamol (OR = 3.58, 95%CI = 1.88–6.82). CTD was associated with NSAIDs and COX-2 inhibitors (OR = 3.08, 95%CI = 1.55–6.14), with oral corticosteroids (OR = 7.15, 95%CI = 3.61–14.14), and with methotrexate (OR = 238, 95%CI = 105.11–538.91). Cancer was associated with cancer drugs (OR = 11.24, 95%CI = 5.90–21.43).

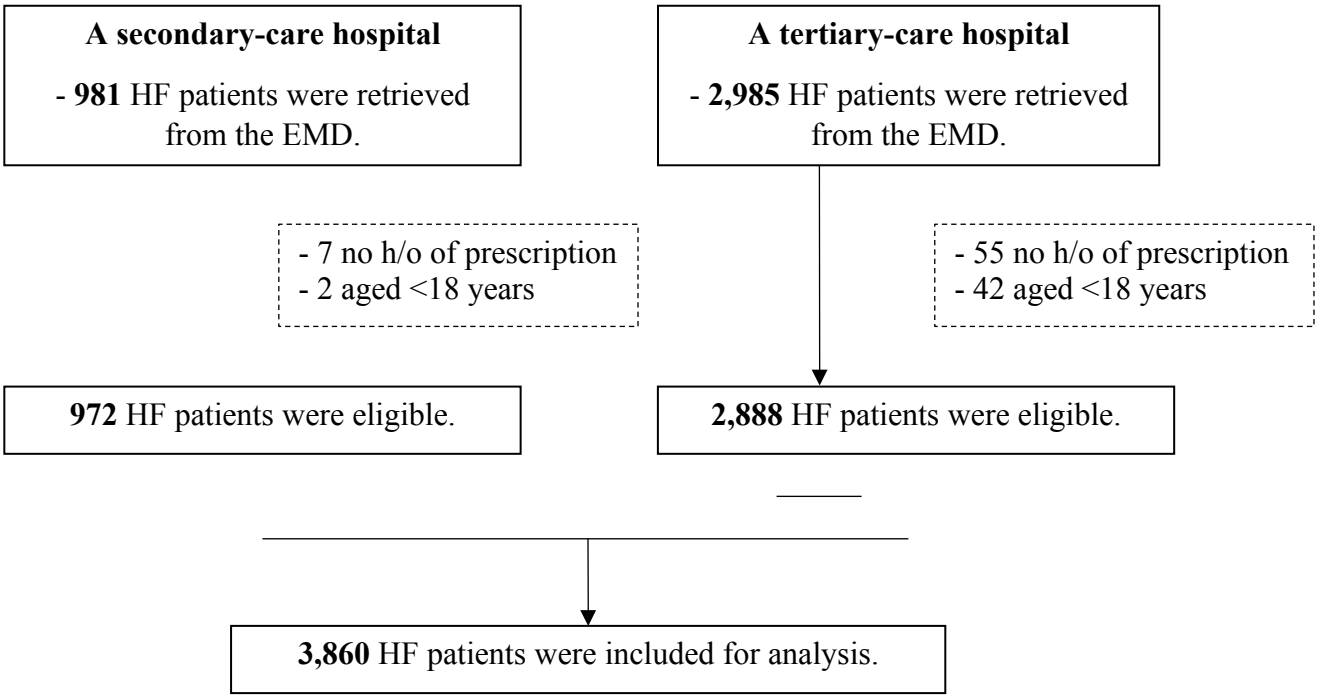

Figure 1 The number of HF patients included in the study

Table 1 Characteristics of the study patients

Characteristics	Total patients (n = 3,860)	Secondary-care hospital (n = 972)	Tertiary-care hospital (n = 2,888)
Demographics			
Female sex	1,948 (50.47)	536 (55.14)	1,412 (48.89)
Age ≥60 years	2,460 (63.73)	683 (70.27)	1,777 (61.53)
Age (in years)	63.62 ± 14.69	65.73 ± 13.65	62.91 ± 14.96
Clinical characteristics			
HFrEF (EF <40%)	816 (32.71)	152 (28.63)	664 (33.81)
HFmrEF (EF 40%–49%)	419 (16.79)	65 (12.24)	354 (18.02)
HFpEF (EF ≥50%)	1,260 (50.50)	314 (59.13)	946 (48.17)
Cardiovascular (CVD) co-morbidities	2,154 (55.80)	624 (64.20)	1,530 (52.98)
Hypertension	1,397 (36.19)	431 (44.34)	966 (33.45)
Ischemic heart diseases	693 (17.95)	144 (14.81)	549 (19.01)
Atrial fibrillation	674 (17.46)	201 (20.68)	473 (16.38)
Cerebrovascular diseases	108 (2.80)	34 (3.50)	74 (2.56)
Peripheral vascular diseases	38 (0.98)	6 (0.62)	32 (1.11)
Number of CVD co-morbidities*	1 (0,1)	1 (0,1)	1 (0,1)
Non-CVD co-morbidities	1,610 (41.71)	534 (54.94)	1,076 (37.26)
Renal failure	813 (21.06)	342 (35.19)	471 (16.31)
Diabetes mellitus	699 (18.11)	177 (18.21)	522 (18.07)
Chronic pulmonary diseases	255 (6.61)	92 (9.47)	163 (5.64)
Dyslipidemia	104 (2.69)	54 (5.56)	50 (1.73)
Cancer	66 (1.71)	16 (1.65)	50 (1.73)
Liver disease	64 (1.66)	31 (3.19)	33 (1.14)
Connective tissue diseases	34 (0.88)	6 (0.62)	28 (0.97)
Osteoarthritis	32 (0.83)	17 (1.75)	15 (0.52)
AIDs	12 (0.31)	5 (0.51)	7 (0.24)
Alzheimer's or dementia	7 (0.18)	0 (0.00)	7 (0.24)
Number of non-CVD co-morbidities	0 (0, 1)	1 (0, 1)	0 (0, 1)
Co-morbidities	3,145 (81.48)	857 (88.17)	2,288 (79.22)
Number of co-morbidities*	3 (1, 4)	3 (2, 5)	3 (1, 4)
Charlson co-morbidity index (CCI) score ≥2	1,616 (41.87)	522 (53.70)	1,094 (37.88)
Heart failure medications			
Diuretic	3,452 (89.43)	902 (92.80)	2,550 (88.30)
BB	1,900 (49.22)	437 (44.96)	1,463 (50.66)
ACEI	1,693 (43.86)	471 (48.46)	1,222 (42.31)
ARB	1,632 (42.28)	333 (34.26)	1,299 (44.98)
CCB	1,562 (40.47)	503 (51.75)	1,059 (36.67)
Nitrate	1,227 (31.79)	163 (16.77)	1,064 (36.84)
MRA	1,153 (29.87)	200 (20.58)	953 (33.00)
Hydralazine	756 (19.59)	159 (16.36)	597 (20.67)
Digoxin	471 (12.20)	169 (17.36)	302 (10.46)
Ivabradine	28 (0.97)	Not available	28 (0.97)
ARNI	6 (0.16)	2 (0.21)	4 (0.14)

*Presented as median and interquartile range (Q_1, Q_3)

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin-II type-1 receptor blocker; BB = beta-blocker; MRA = mineralocorticoid receptor antagonist; CCB = calcium channel blocker; ARNI = angiotensin receptor neprilysin inhibitor
Ejection fraction (EF) were available for 531 and 1,964 patients at a secondary- and a tertiary-care hospital, respectively.

Table 2 Distribution of each PIMHF item in each study hospital

Secondary-care hospital (n = 972)			Tertiary-care hospital (n = 2,888)		
PIMHF item*	**n**	**%**	**PIMHF item***	**n**	**%**
Prescribed with any PIMHF	439	45.16	Prescribed with any PIMHF	955	33.07
Prednisolone	224	23.05	Prednisolone	340	11.77
Naproxen	133	13.68	Diclofenac	281	9.73
Diclofenac	81	8.33	Naproxen	220	7.62
Ibuprofen	75	7.72	Pioglitazone	176	6.09
Pioglitazone	64	6.58	Ibuprofen	166	5.75
Salbutamol	47	4.84	Cyclophosphamide	48	1.66
Prazosin	21	2.16	Pseudoephedrine	41	1.42
Celecoxib	15	1.54	Dexamethasone	37	1.28
Methotrexate	10	1.03	Etoricoxib	27	0.93
Ergotamine plus Caffeine	8	0.82	Prazosin	26	0.90
Pseudoephedrine	4	0.41	Methotrexate	26	0.90
Clozapine	4	0.41	Celecoxib	26	0.90
Verapamil	2	0.21	Clozapine	22	0.76
Cyclophosphamide	2	0.21	Doxorubicin	19	0.66
Indomethacin	2	0.21	Paclitaxel	16	0.55
Diltiazem immediate release	0	0.00	Salbutamol	14	0.48
Terbutaline	0	0.00	Ergotamine plus Caffeine	8	0.28
Lithium	0	0.00	Piroxicam	5	0.17
Dexamethasone	0	0.00	Verapamil	4	0.14
Hydrocortisone	0	0.00	Melphalan	4	0.14
Piroxicam	0	0.00	Fluorouracil (5-FU)	4	0.14
Flecainide	N/A		Trastuzumab	4	0.14
Diltiazem slow release	N/A		Docetaxel	3	0.10
Sildenafil	N/A		Diltiazem slow release	2	0.07
Clonidine	N/A		Sildenafil	2	0.07
Fludrocortisone	N/A		Indomethacin	2	0.07
Busulfan	N/A		Chlorambucil	1	0.03
Chlorambucil	N/A		Mitomycin	1	0.03
Melphalan	N/A		Capecitabine	1	0.03
Carmustine	N/A		Lithium	0	0.00
Ifosfamide	N/A		Dactinomycin	0	0.00
Procarbazine	N/A		Mercaptopurine(6-MP)	0	0.00
Bleomycin	N/A		Idarubicin	0	0.00
Dactinomycin	N/A		Bleomycin	0	0.00
Mitomycin	N/A		Ifosfamide	0	0.00
Doxorubicin	N/A		Fludrocortisone	0	0.00
Idarubicin	N/A		Flecainide	N/A	
Mitoxantrone	N/A		Diltiazem immediate release	N/A	
Fluorouracil (5-FU)	N/A		Terbutaline	N/A	
Mercaptopurine(6-MP)	N/A		Clonidine	N/A	
Capecitabine	N/A		Hydrocortisone	N/A	
Paclitaxel	N/A		Busulfan	N/A	
Docetaxel	N/A		Carmustine	N/A	
Trastuzumab	N/A		Procarbazine	N/A	
Etoricoxib	N/A		Mitoxantrone	N/A	
Dronedarone	N/A		Dronedarone	N/A	
Pramipexole	N/A		Pramipexole	N/A	

*Listed by frequency in descending order

N/A = Not available

Diltiazem (immediate & slow release) and verapamil were considered PIMHF when used in HFrEF. Sildenafil were considered PIMHF when used with nitrates.

Table 3 Crude odds ratio (crude ORs) and 95% confidence interval (95% CI) of potential factors associated with PIMHF use

Potential factors	Crude ORs (95% CI)	P-value
Female sex	1.18 (1.04 – 1.35)	0.012*
Age ≥60 years	1.18 (1.03 – 1.35)	0.019*
Cardiovascular (CVD) co-morbidities	1.06 (0.93 – 1.21)	0.414
Hypertension	1.31 (1.14 – 1.50)	<0.001*
Ischemic heart diseases	0.96 (0.81 – 1.14)	0.645
Cerebrovascular diseases	0.96 (0.64 – 1.43)	0.839
Atrial fibrillation	0.79 (0.66 – 0.94)	0.010*
Peripheral vascular diseases	0.72 (0.36 – 1.45)	0.357
Number of CVD co-morbidities	1.03 (0.95 – 1.12)	0.467
Non-CVD co-morbidities	1.81 (1.58 – 2.06)	<0.001*
Diabetes mellitus	1.65 (1.40 – 1.95)	<0.001*
Dyslipidemia	0.93 (0.62 – 1.41)	0.747
Renal failure	1.34 (1.15 – 1.57)	<0.001*
Alzheimer's or dementia	1.33 (0.30 – 5.94)	0.711
Chronic pulmonary diseases	2.57 (1.99 – 3.33)	<0.001*
Connective tissue diseases	6.94 (3.01 – 15.97)	<0.001*
Osteoarthritis	1.57 (0.78 – 3.15)	0.207
Liver	1.06 (0.64 – 1.77)	0.816
Cancer	1.90 (1.17 – 3.10)	0.010*
AIDs	2.48 (0.79 – 7.84)	0.121
Number of non-CVD co-morbidities	1.53 (1.40 – 1.68)	<0.001*
Co-morbidities	1.13 (0.95 – 1.34)	0.162
Number of co-morbidities	1.08 (1.04 – 1.12)	<0.001*
Charlson co-morbidity index (CCI) score ≥2	1.76 (1.54 – 2.01)	<0.001*

*Factors with p-values less than 0.05 were incorporated into a multivariate analysis.

In the multicollinearity test, the number of non-CVD co-morbidities and a CCI score ≥2 were highly correlated with non-CVD co-morbidities, with Pearson's correlation coefficients (r) equal to 0.89 and 0.86, respectively.

Discussion

Our findings revealed that PIMHF use was highly prevalent in real clinical practice and was significantly associated with non-CVD co-morbidities present in HF patients.

The prevalence of overall PIMHF use at both secondary- (45.16%) and tertiary-care hospitals (33.07%) was greater than that in a similar study by Bermingham, who reported a prevalence of 14.6% among HF outpatients.[22] Such a difference in prevalence resulted primarily from the different list of PIMHF used in detecting PIMHF. St Vincent's list of 11 PIMHF was used in Bermingham's study[22], whereas the Thailand list of PIMHF containing 47 PIMHF items was used in our study.[23] Thus, the chance of finding HF patients receiving PIMHF was greater in our study.

The prevalence of overall PIMHF use was higher in the secondary-care hospital than in the tertiary-care hospital. This may have been due to differences in the prevalence of co-morbidities. As multiple co-morbidities lead to a greater requirement for the prescription of multiple medications[18, 19], the number of co-morbidities in the patient sample can directly affect the prevalence of PIMHF use. Our study showed that the proportion of patients with ≥1 co-morbidity was higher in a secondary-care hospital than in a tertiary-care hospital (88.17% vs. 79.22%). Such a difference was also found in both CVD co-morbidities (64.20% vs. 52.98%) and non-CVD co-morbidities (54.94% vs. 37.26%).

Regarding co-morbidities accompanying HF, overall, greater than three-fourths of the patients (81.48%) had at least one co-morbidity, and 13.45%, 13.76%, and 68.03% had one, two, and 2 co-morbidities, respectively. These findings were consistent with a recent European survey suggesting that three-fourths of patients had at least one co-morbidity, and 30%, 23%, and 43% had one, two, and 2 co-morbidities, respectively.[12] In addition to CVD co-morbidities, several non-CVD co-morbidities were found in this study, consistent with a previous study reported by Page et all, which compiled the studies on co-morbidities in HF patients, including renal failure, diabetes mellitus, asthma and COPD, cancer, osteoarthritis or arthritis, and Alzheimer's or dementia.[13]

The distribution of prescribed PIMHF items was found to be similar between the two study hospitals. The most frequently prescribed PIMHF found in our study was oral corticosteroids (15.6%), including prednisolone (14.61%) and dexamethasone (0.96%), consistent with the studies of Bermingham (17.5%)[22] and Masoudi (18.9%).[20] This medication class was found to be associated with non-CVD co-morbidities, including CPD and CTD. As all oral corticosteroids are considered as PIMHF and may have no substitutes,

clinical parameters indicating sodium and fluid retention (e.g., weight and blood pressure) should be closely monitored while using these medications. Pioglitazone, one of thiazolidinediones, came in second with a prevalence of 6.22%, consistent with the study by Masoudi et al. (6.9%).[20] According to Thailand's HF guidelines, thiazolidinediones are not recommended in HF patients due to the increased risk of worsening HF and hospitalization. In treating diabetes mellitus in HF patients, metformin should be used as a first-line therapy unless contraindicated.[30] Thus, the use of pioglitazone should be avoided, and metformin should be considered a substitute. NSAIDs and COX-2 inhibitors were found to be prescribed in our study, whereas none of the patients in Bermingham's study were using NSAIDs or COX-2 inhibitors.[22] NSAIDs and COX-2 inhibitors not only have harmful effects on HF (e.g., including promotion of fluid retention, blood pressure elevation), but also on patients with cardiovascular disease (e.g., adverse cardiovascular outcomes and bleeding complications). Thus, it remains important to limit their use when possible.[31] If necessary, naproxen appears to be considered safer than other NSAIDs and COX-2 inhibitors because it has low COX-2 selectivity, demonstrating greater selectivity for COX-1 inhibition, resulting in a favorable thromboembolic and overall cardiovascular safety profile.[32, 33] Non-DHP CCBs (26.3%) were the most prescribed PIMHFs in the Bermingham study[22], whereas only eight patients with HFrEF prescribed non-DHP CCBs were found in our study. Most of the HF patients (65.5%) in our study had ejection fraction (EF), so it was likely that the physicians avoided prescribing non-DHP CCBs in patients with HFrEF. The other prescribed PIMHF items, including salbutamol (1.58%), clozapine (0.67%), and prazosin (1.22%), were consistent with a previous report by Masoudi et al.[20]

Our study also supported the relationship of non-CVD co-morbidities with overall and specific PIMHF use. Among non-CVD co-morbidities, CTD appeared to be the most influenced factor, with an OR of 7.16, as it was associated with several PIMHF items, including oral corticosteroids, NSAIDs/COX-2 inhibitors, and methotrexate.

There were several strengths of our study. First, the prevalence of PIMHF use was studied using real data from a large HF population and presented by hospital level. Second, the patient data used were obtained from the EMD, which contains comprehensive clinical and prescribed medication data. Third, several ICD-10 codes relevant to HF were used to identify HF patients.

There were some limitations to our study. Only 29 of 47 PIMHF items were assessed, so the prevalence of the remaining 18 PIMHF items still cannot be concluded. Data on disease severity, such as the New York Heart Association (NYHA) classification, were

lacking, so whether patients with and without PIMHF had different severities, which could be related to PIMHF use, was unknown. The findings of our study should probably not be generalized to other settings with different PIMHF items and prescribing practices.

In conclusion, PIMHF use according to the Thailand list of PIMHF was highly prevalent in both secondary- and tertiary-care hospitals. A careful prescription and a thorough review of medication use through some mechanisms, e.g., medication reconciliation (MR) and computerized provider order entry with clinical decision support (CPOE/CDS), are required to limit PIMHF use. The strategy should be at least focused on HF patients with DM, CPD, CTD, and cancer.

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