Prescription of Potentially Harmful Drugs in Young Adults With Heart Failure and Reduced Ejection Fraction

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According to national guidelines and statements drugs that can cause or exacerbate heart failure (HF) are considered potentially harmful and should be avoided if possible in patients with a diagnosis of heart failure with reduced ejection fraction (HFREF). To evaluate the prevalence of potentially harmful drug (PHD) prescription among patients with a diagnosis of systolic heart failure we conducted a retrospective cohort study using Truven Health MarketScan Commercial database from 2011 to 2014. Prescription of PHD as defined by American Heart Association Statement was examined among patients with a HFREF diagnosis in: (1) Two outpatient encounters, (2) One inpatient encounter as primary diagnosis and/or (3) one inpatient encounter any position and one outpatient encounter. Among 40,966 patients, 24.2% were prescribed with at least 1 drug with the potential to cause or exacerbate heart failure. Of the 9,954 patients prescribed with PHD, nonsteroidal anti-inflammatory agents were the most frequent category prescribed (67.4%), followed by antihypertensive (24%), diabetes mellitus (23.3%), neurological and psychiatric (21%) and antiarrhythmic medications (12.6%). After multivariable analysis female patients, the presence of a comorbidity associated with a PHD use and polypharmacy were more frequently prescribed a PHD. In conclusion almost ¼ of adult patients with a diagnosis of HFREF have a prescription of a drug with a potential to cause or exacerbate heart failure as defined by current heart failure guidelines. **(Am J Cardiol 2019;123:1458−1463)**

Advances in pharmacology, device therapy, and mechanical support have reduced mortality in patients with heart failure with reduced ejection fraction (HFREF).[1−4] Multimorbidity and polypharmacy is frequent among patients with HFREF.[5−8] Nonsteroidal anti-inflammatory agents, nondihydropiridine calcium channel blockers, thiazolidinediones, and antiarrhythmics (dronedarone, sotalol, and flecainide) have a class III recommendation in most recent heart failure guidelines.[9] In 2016 the American Heart Association published a statement providing an evidence based list of drugs that may cause or exacerbate heart failure.[10] The epidemiology of this problem is poorly described in contemporary literature. Therefore we sought to investigate (1) the prevalence of potentially harmful drug (PHD) prescription in patients with a diagnosis systolic heart failure, (2) identify the most frequent PHDs prescribed and (3) describe patient and care characteristics most frequently associated with exposure to PHD.

Methods

A retrospective, observational study was conducted to select patients with a diagnosis of systolic heart failure using administrative medical claims from Truven Health Market Scan Claims database for years 2011 to 2015.

Patients who were 18 years old or older and less than 65 years old with a non-Health Maintenance Organization type of plan were included in the study if they had a diagnosis of Systolic Heart Failure defined as an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM): 428.1, 428.20, 428.21, 428.22, 428.23, 428.40, 428.41, 428.42, and 428.43 present in: (1) Two outpatients encounters, (2) one inpatient encounter as primary diagnosis or (3) one inpatient encounter (HF diagnosis in any position), and one outpatient encounter diagnosis. Data for these patients were then extracted for all available years and checked for presence or not of outpatient pharmacy claims for PHD. These represent medications bought by patients and for which a claim was submitted at retail pharmacies or mail specialty pharmacies.

The latest encounter date with a diagnosis of HFREF was the enrollee's inclusion date. Encounter dates had to be after June 30th, 2011 so that the exclusion criteria (chronic obstructive pulmonary disease on steroids, end stage renal disease or malignant neoplasm with/without metastatic disease) could be checked 6 months back. Enrollees with less than 6 months of previous enrollment from the inclusion date and no pharmacy coverage from the inclusion date were also excluded. Individuals were

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See page 1462 for disclosure information.

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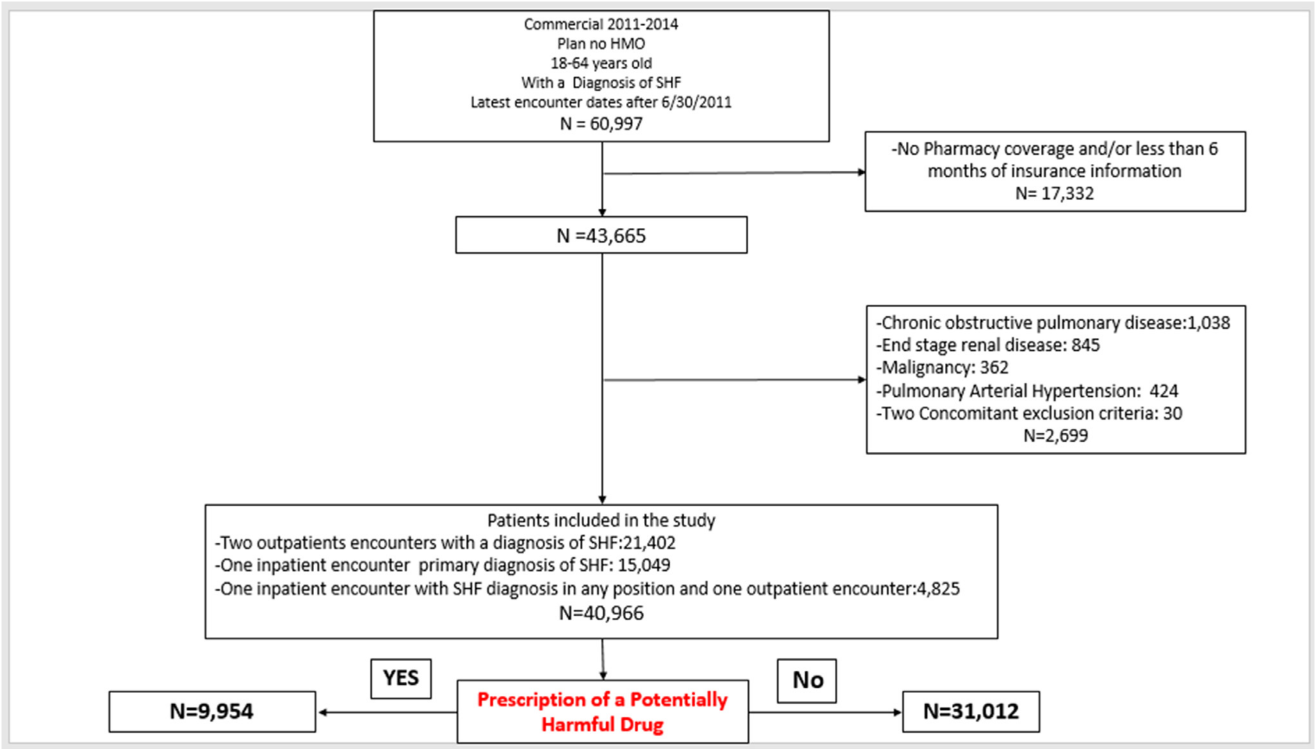

Figure 1. Flow diagram of analyzed cohort.

then followed from their inclusion date until the end of the study (December 31st, 2014) for a PHD event. The first PHD event date was the enrollee's index date. PHDs were defined as oral medications with a major potential for induction or precipitation of heart failure and level of evidence A or B according to AHA Scientific Statement.[10] Anticancer drugs were excluded. The drugs were included in the following categories: Nonsteroidal anti-inflammatory agents(NSAID), diabetes mellitus medications (thiazolidinediones, saxagliptin, and sitagliptin), antiarrhythmic medications (flecainide, disopyramide, sotalol and dronedarone), antihypertensive medications (doxazosin, diltiazem, verapamil), hematologic medications (cilostazol), neurological and psychiatric medications (Stimulants: racemic amphetamine, dextroamphetamine, methylphenidate, methamphetamine, pseudoephedrine; antidepressants: citalopram; antiparkinsonian: bromocriptine,

Table 1
Patient population characteristics, exposed and nonexposed

	All (n = 40,966)	Not exposed (n = 31,012)	Exposed (n = 9,954)	p Value
Age (years)				
18-30	977 (2.4 %)	804 (2.6%)	173 (1.7%)	<.0001
31-50	9,195 (22.4%)	7,009 (22.6%)	2,186 (22%)	
51-64	30,794 (75.2%)	23,199 (74.8%)	7,595 (76.3%)	
Male	26,073 (63.6%)	20,043 (64.6%)	6,030 (60.6%)	<.0001
Female	14,893 (36.4%)	10,969 (35.4%)	3,924 (39.4%)	
Diabetes mellitus	20,215 (49.3%)	14,402 (46.4%)	5,813 (58.4%)	<.0001
Hypertension	35,470 (86.6%)	26,412 (85.2%)	9,058 (91%)	<.0001
Obesity	13,023 (31.8%)	9,179 (29.6%)	3,844 (38.6%)	<.0001
Atrial fibrillation	14,059 (34.3%)	10,185 (32.8%)	3,874 (38.9%)	<.0001
Chronic renal failure	11,634 (28.4%)	8,856 (28.6%)	2,778 (27.9%)	0.203
Myocardial infarction	12,709 (31%)	9,873 (31.8%)	2,836 (28.5%)	<.0001
Peripheral vascular disease	9,796 (23.9%)	7,186 (23.2%)	2,610 (26.2%)	<.0001
Stroke	4,107 (10%)	3,089 (10%)	1,018 (10.2%)	0.446
Chronic obstructive pulmonary disease	19,675 (48%)	14,568 (47%)	5,107 (51.3%)	<.0001
Collagen vascular diseases	3,380 (8.3%)	2,299 (7.4%)	1,081 (10.9%)	<.0001
Osteoarthritis	9,373 (22.9%)	6,160 (19.9%)	3,213 (32.3%)	<.0001
Attention deficit/hyperactivity disorder	443 (1.1%)	230 (0.7%)	213 (2.1%)	<.0001
Depression	9,856 (24.1%)	6,768 (21.8%)	3,088 (31%)	<.0001
Narcolepsy	80 (0.2%)	40 (0.1%)	40 (0.4%)	<.0001
Psychoses	1,802 (4.4%)	1,277 (4.1%)	525 (5.3%)	<.0001
Drug Abuse	1,779 (4.3%)	1,244 (4%)	535 (5.4%)	<.0001

pramipexole, appetite suppressants: phentermine) and pulmonary medications (bosentan). Drugs were identified using National Drug Code (NDC). Individuals were flagged as exposed to a PHD starting at the time of the first individual dispensing (index date) of a (PHD).

Other covariates evaluated included baseline demographic (age, sex, region) information from enrollment files and comorbidities including diabetes, atrial fibrillation, osteoarthritis, rheumatoid arthritis/collagen vascular diseases, psychoses, depression, attention-deficit/hyperactivity disorder among others. The presence of guideline-directed medical therapy for HFREF defined as the concomitant administration of angiotensin converting enzyme inhibitor or angiotensin receptor blocker and a beta-blocker and implantable cardioverter defibrillator (ICD) were evaluated. Also, we assessed whether patients had a cardiologist involved in their care. Cardiologist visit was identified reviewing professional claims and assumed if the physician involved had a specialty identified as "Cardiologist" in the claims dataset.

We compared demographic characteristics, comorbid diseases, medication use, among patients with HFREF with or without prescription of PHD, by the use of chi-square test for categorical variables and independent sample t test or Wilcoxon rank-sum test (as appropriate) for continuous variables. We created multivariate logistic regression models with dependent variable the exposure to PHD and independent variables demographic such as age and gender, clinical characteristics including osteoarthritis, hypertension, diabetes, atrial fibrillation, myocardial Infarction, peripheral vascular disorders, chronic obstructive pulmonary disease (COPD) and neurological and/or psychiatric disorders and medical utilization parameters including outpatient cardiology follow up, presence of polypharmacy, use of loop diuretics, and guideline directed medical therapy. The results of regression analyses were reported as odds ratios (ORs) with 95% confidence intervals (CIs) for the presence of absence of PHD in HFREF. All analyses were conducted with the use of SAS with 2-tailed level of significance set at 0.05.

The research protocol was approved by the University of Texas Health Science Center institutional review board.

Results

The study included 40,966 patients. Figure 1 shows the identification and inclusion process. The majority of patients were included in our analytical cohort due to having 2 or more outpatient visits with a HFREF diagnosis (52.2%), followed by 1 or more inpatient episodes for HFREF (34.8%) and a combination of inpatient episode with HFREF as a secondary diagnosis and at least one outpatient visit due to HFREF (13%). (Table 1) The average follow-up time was 9.29 months. Baseline demographic and clinical characteristics are presented on Table 1.

A total of 9,954 (24.3%) patients filled a prescription for a PHD during the study period (Figure 1 and Table 1). The unadjusted analysis showed statistically significant differences between those prescribed a PHD versus those not prescribed a PHD. Patients on PHD were more likely to be female (35.4% vs 39.4%) and had higher prevalence of comorbidities (no PHD vs. PHD: diabetes 46.4% vs 58.4%, hypertension 85.2% vs 91%, obesity 29.6% vs 38.6%, atrial fibrillation 32.8% vs 38.9%, PVD 23% vs 26.2%, COPD 47% vs 51.3%, osteoarthritis 19.9% vs 32.3%). Those prescribed PHD were also more likely to suffer osteoarthritis (no PHD vs PHD 19.9% vs 32.2%) and certain psychiatric and neurological disorders such as depression (21.8% vs 31%).

Of the 9,954 patients exposed to PHD, NSAIDs agents were the most frequent category prescribed (67.4%), followed by antihypertensive (24%), diabetes mellitus (23.3%), neurological and psychiatric (21%), and antiarrhythmic medications (12.6%) while less than 2% of were exposed to other groups of PHD (e.g. cilostazol) (Table 2). Figure 2 shows the number of patients and prescriptions of PHD in the study cohort. The majority of patients who received a PHD were prescribed more than once a

Table 2
Potentially harmful drugs prescribed in patients with a diagnosis of systolic heart failure

Prescription dispensed	n = 15,237
Nonsteroidal anti-inflammatory drugs	**6,710 (44.0%)**
Diclofenac	1,690 (11.1%)
Ibuprofen	1618 (10.6%)
Naproxen	872 (5.7%)
Meloxicam	803 (5.3%)
Indomethacin	540 (3.5%)
Celecoxib	376 (2.5%)
Ketorolac	356 (2.3%)
Etodolac	147 (1.0%)
Nabumetone	126 (0.8%)
Other	182 (1.2%)
Antihypertensive medications	**2,396 (15.7%)**
Diltiazem	1,675 (11.0%)
Doxazosin	438 (2.9%)
Verapamil	283 (1.9%)
Diabetes mellitus medications	**2,326 (15.3%)**
Sitagliptin	1,438 (9.4%)
Pioglitazone	574 (3.8%)
Saxagliptin	285 (1.9%)
Rosiglitazone	29 (0.2%)
Neurological and psychiatric medications	**2,364 (15.5%)**
Stimulants	***320 (2.1%)***
Amphetamine salt combination	181 (1.2%)
Methylphenidate	122 (0.8%)
Other	17 (0.1%)
Antidepressants	***1,680 (11.0%)***
Citalopram	1,680 (11.0%)
Antiparkinsonian medications	***308 (2.0%)***
Pramipexole	279 (1.8%)
Bromocriptine	29 (0.2%)
Appetite suppressants	***56 (0.4%)***
Phentermine	56 (0.4%)
Antiarrhythmic medications	**1,258 (8.3%)**
Sotalol	798 (5.2%)
Dronedarone	266 (1.7%)
Flecainide	179 (1.2%)
Disopyramide	15 (0.1%)
Hematologic medications	**154 (1.0%)**
Cilostazol	154 (1.0%)
Pulmonary medications	**29 (0.2%)**
Bosentan	29 (0.2%)

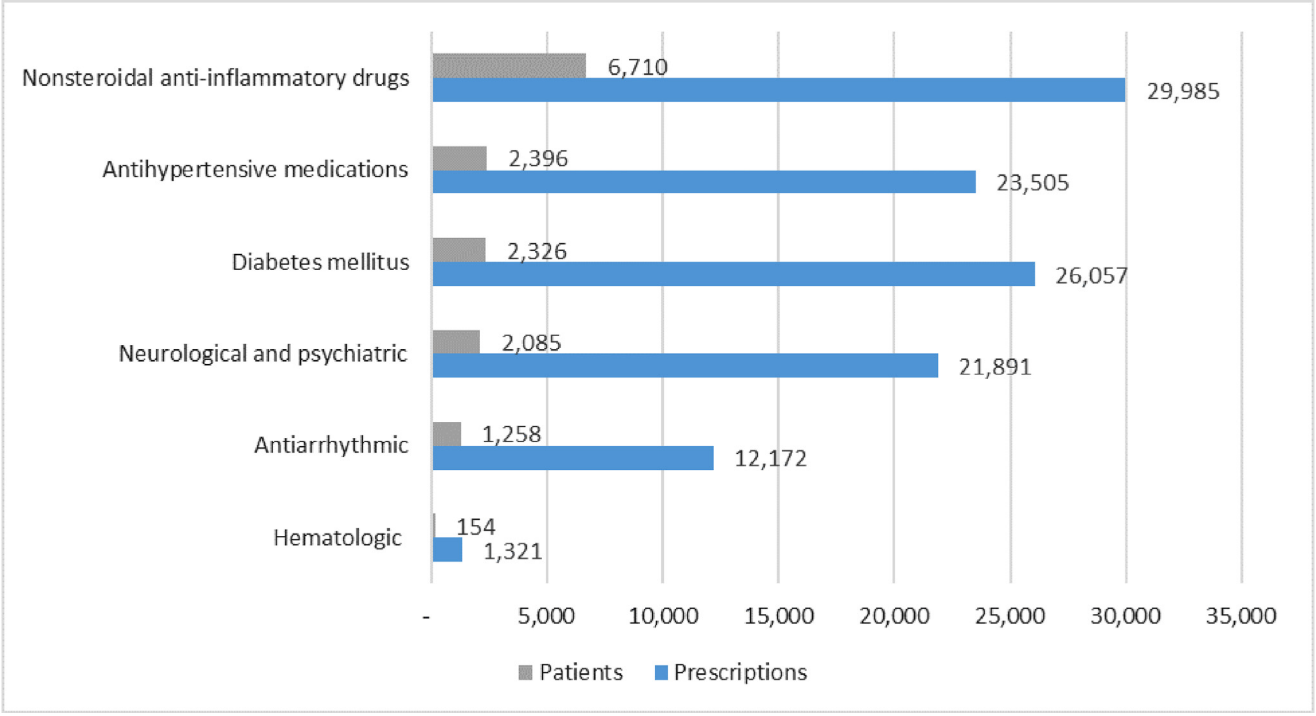

Figure 2. Number of prescription and patients exposed to potentially harmful drugs.

potentially harmful drug. For instance, there were 6,710 individuals who were prescribed and filled at least one NSAID medication, but the total number of NSAID medications prescribed was 29,985. This accounted for approximately 4.5 NSAID prescriptions per person prescribed an NSAID.

Table 3 describes adherence to guideline treatment for the overall population as well as both, the exposed and unexposed groups. Our multivariate analysis suggested that female gender (OR, 1.16; 95%CI, 1.10 to 1.22), presence of comorbidities including osteoarthritis (OR, 1.7; 95%CI, 1.61 to 1.79), hypertension (OR, 1.36; 95%CI, 1.25 to 1.47), diabetes (OR, 1.52 95%CI, 1.44 to 1.59), atrial fibrillation (OR, 1.23, 95%CI 1.17 to 1.290), and neurological and/or psychiatric disorders (OR 1.42; 95%CI, 1.35 to 1.50) were associated with higher risk of PHD prescription. In contrast, history of myocardial infarction (OR 0.76, 95%CI, 0.72 to 0.80) and treatment with guideline-directed medical therapy (OR, 0.90; 95%CI, 0.85 to 0.95) were associated with lower risk of PHD prescription. Prescription of five or more medications (OR 1.69; 95%CI 1.59 to 1.79) and having at least one visit to a cardiologist was (OR, 1.74; 95%CI, 1.65 to 1.84) associated with higher likelihood of receiving a PHD after multivariate adjustment. (Table 4) Finally, receiving guideline directed medical therapy had a negative association with PHD exposure.

Discussion

Our study shows that approximately 1/4 of patients with a diagnosis of heart failure and reduced ejection fraction are exposed to medications that can exacerbate heart failure. NSAIDs were the most frequently prescribed PHD in our study. Higher comorbidity burden and polypharmacy were associated with the use of PHD. The adverse cardiovascular consequences of NSAID use have been reviewed

Table 3
Heart failure therapies, cardiologist involvement and polypharmacy

	All (n = 40,966)	Not exposed (n = 31,012)	Exposed (n = 9,954)	p Value
Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers	31,820 (77.7%)	23,798 (76.7%)	8,022 (80.6%)	<.0001
Beta blockers	33,407 (81.5%)	25,196 (81.2%)	8,211 (82.5%)	0.005
Aldosterone Antagonists	14,815 (36.2%)	11,325 (36.5%)	3,490 (35.1%)	0.008
loop diuretics	28,432 (69.4%)	21,156 (68.2%)	7,276 (73.1%)	<.0001
Implantable cardioverter defibrillator	2,834 (6.9%)	2,197 (7.1%)	637 (6.4%)	0.023
Cardiologist care	28,432 (69.4%)	20,659 (66.6%)	7,773 (78.1%)	<.0001
polypharmacy (>5 medications)	7,039 (17.2%)	4,546 (14.7%)	2,493 (25.0%)	<.0001
Excessive polypharmacy (>10 medications)	1,528 (3.7%)	843 (2.7%)	685 (6.9%)	<.0001
Guideline directed medical therapy	28,896 (70.5%)	21,836 (70.4%)	7,060 (70.9%)	0.327

Table 4
Multivariable logistic regression analysis for potentially harmful drug prescription

	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Age, years		
18-30	0.66 (0.56-0.78)	1.00 (ref)
31-50	0.96 (0.91-1.02)	1.12 (0.94-1.34)
51-64	1.08 (1.03-1.14)	1.01 (0.85-1.20)
Male	0.84 (0.80-0.88)	1.00 (ref)
Female	1.19 (1.14-1.25)	1.16 (1.10-1.22)
Osteoarthritis	1.92 (1.83-2.02)	1.70 (1.61-1.79)
Hypertension	1.76 (1.63-1.90)	1.36 (1.25-1.47)
Diabetes mellitus	1.62 (1.55-1.69)	1.52 (1.44-1.59)
Atrial fibrillation	1.30 (1.24-1.37)	1.23 (1.17-1.29)
Myocardial infarction	0.85 (0.81-0.90)	0.76 (0.72-0.80)
Peripheral vascular disorders	1.18 (1.12-1.24)	0.99 (0.94-1.04)
Chronic obstructive pulmonary disease	1.19 (1.14-1.24)	1.01 (0.96-1.06)
Neurological and/or psychiatric disorders *	1.58 (1.51-1.66)	1.42 (1.35-1.50)
Outpatient cardiology visit	1.79 (1.69-1.88)	1.74 (1.65-1.84)
Polypharmacy	1.95 (1.84-2.06)	1.69 (1.59-1.79)
Guideline directed medical therapy	1.03 (0.98-1.08)	0.90 (0.85-0.95)
Loop diuretics	1.27 (1.20-1.33)	1.05 (0.99-1.11)

* Attention deficit/hyperactivity disorder; depression; narcolepsy and psychoses.

recently.[11] We have previously reported that the inpatient use of NSAID in patients with heart failure was infrequent (approximately 4%) but associated with worse outcomes including longer length of stay (7.0 ± 8.8 days vs 6.1 ± 8.5 days) and increased prevalence of worsening renal function (34.4% vs 27.9%).[12,13] Although more than 50% of the patients exposed to PHD were prescribed an NSAID this is underestimation of NSAID use given their over the counter availability. Interestingly, outpatient cardiology visits were recorded in the majority of patients included in the study (approximately 70%). Nevertheless, after adjusting for covariates the outpatient cardiology visits were more frequent in patients exposed to PHD. We believe that this finding reflects higher prevalence of comorbidities that required frequent follow-up with a cardiologist.

Because our study relied exclusively upon claims data to identify diagnoses and medications errors in coding or non-submission may have resulted in inaccurate classification of patients. The use of diagnostic codes has been shown to be accurate in cardiovascular diagnosis. We did not have access to left ventricular ejection fraction, and this may represent a limitation given that the recommendations of AHA guidelines applied to patients with heart failure and reduced ejection fraction. Nevertheless, previous studies have used a similar approach (using ICD 9 codes for HFREF) to identify patients with this condition.[14] In addition only patients younger than 65 years old were included. Patients with systolic heart failure were included but data is not applicable to patients with heart failure and preserved ejection fraction. Duration of medication exposure is not evaluated because of database-based analysis. Over the counter use of NSAIDs were not included because only prescribed medications were evaluated for data analysis. It is important to emphasize that the absence of variables related to the severity of heart failure (e.g. NYHA) and comorbid conditions (e.g. severity of pain related to osteoarthritis, chronic obstructive pulmonary disease) precludes a risk/benefit analysis of the prescription of PHD in individual patients and expected desirable effects of those medications

The prescription of potentially harmful drugs among adult patients with systolic heart failure is frequent. Adherence to the ACC/AHA guidelines and careful review of medication lists by prescribing physicians and especially cardiologists is crucial. Furthermore, monitoring strategies should be incorporated in electronic medical records and prescription systems to detect and prevent if possible prescription of PHD.

Disclosures

The authors have no conflicts of interest to disclose.

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