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Increased Fracture Risk with Furosemide Use in Children with Congenital Heart Disease

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Abstract

Objectives—To determine the association of furosemide therapy with the incidence of bone fractures in children with congenital heart disease (CHD).

Study design—We conducted a retrospective cohort study with data extracted from 2008–2014 Texas Medicaid databases. Pediatric patients aged <12 years diagnosed with CHD, cardiomyopathy, or heart failure were included. Patients taking furosemide were categorized into a Furosemide-Adherent group (Medication Possession Ratio (MPR) ≥70%), and a Furosemide Non-adherent group (MPR<70%). A third group of patients was matched to the furosemide user groups by employing propensity score matching. A multivariate logistic regression and Cox proportional hazard model with a Kaplan–Meier plot (time-to-fracture) were used to compare the 3 groups, controlling for baseline demographics and clinical characteristics.

Results—After matching, 3,912 patients (Furosemide-Adherent: n=254, Furosemide Non-Adherent: n=724, No Furosemide: n=2,934) were identified. The incidence of fractures was highest for the Furosemide-Adherent group (9.1%; 23/254), followed by the Furosemide Non-Adherent group (7.2%; 52/724), which were both higher than for patients who did not receive furosemide (5.0%; 148/2,934) ($p < 0.001$). Using logistic regression, both furosemide groups were more likely to have fractures than the No Furosemide group; Furosemide-Adherent OR=1.9 (95% CI: 1.17–2.98, $P = .009$); Furosemide Non-Adherent OR=1.5 (95% CI: 1.10–2.14, $p = 0.01$). In the Cox proportional hazard model, the risk of fractures for the Furosemide-Adherent group was

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significantly higher compared with the No Furosemide group (HR=1.6; 95% CI: 1.00–2.42, $p=0.04$).

Conclusions—Furosemide therapy, even with non-consistent dosing, was associated with an increased risk of bone fractures in children with CHD.

Keywords

furosemide; loop diuretic; congenital heart disease; fractures

Furosemide, a potent diuretic, increases the urinary loss of potassium, calcium, and magnesium by inhibiting the passive re-absorption of these ions in the Loop of Henle of the kidney.^{2,3} Furosemide can thus cause hypercalciuria and nephrocalcinosis.⁴ The excretion of calcium in the urine may cause a loss of bone mineral density (BMD) which can lead to osteoporosis.^{5–7} An observational study indicated that for the adult population studied, any use of loop diuretics was associated with an increased risk of any fracture (crude 51% [OR=1.51; 95% CI=1.48–1.55]; adjusted 4% [OR=1.04; CI=1.01–1.07]).⁸ In a meta-analysis that studied the association between loop diuretic uses and the risk of fractures for adult patients, compared with non-loop diuretic users, loop diuretics users had an approximately 15% higher risk of total fractures.⁹

Furosemide is less commonly prescribed in children than adults. Specific children, including those with congenital heart defects (CHD), have a higher use of this medication.² More specifically, in children who have CHD and cardiomyopathies, diuretics often are given to treat symptoms of heart failure.¹⁰ However, given studies conducted in adults with furosemide use, concerns remain about loop diuretics, particularly with chronic use, for children. Furosemide is specifically related to higher rates of hypercalciuria.¹¹ Atkinson et al reported that treatment with any type of diuretic in infants was associated with an abnormal renal loss of calcium, sodium, chloride, and potassium and others have cautioned that children with CHD or who have cardiomyopathy and who are prescribed loop diuretics may be at particular risk for developing metabolic bone disease (MBD).¹²

The purpose of this study was to determine the association of furosemide therapy with fractures in children with CHD.

Methods

Data were extracted from the Texas Medicaid Database, which consists of insurance claims that include demographic, medical, and prescription claims between January 1, 2008 and December 31, 2014. The Texas Medicaid program provides health insurance coverage for low-income families, individuals with chronic disabilities, blind persons, low-income pregnant women, elderly people or seniors, non-disabled children, and caretakers of dependent children. Medicaid enrollment in the state of Texas for clients under 21 is approximately 3 million for 2016.¹³

The study was approved by the University of Texas at Austin Institutional Review Board and by the Texas Health and Human Services Commission. The following information was extracted from the Texas Medicaid database: date of birth, sex, race/ethnicity, start and end

dates of health plan enrollment, *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnostic codes, Healthcare Common Procedure Coding System (HCPCS) codes, service dates, quantity of the medication dispensed, the number of days of supply, National Drug Code (NDC), Generic Sequencing Number (GCN), and American Hospital Formulary Service (AHFS) number.

Study Design

A retrospective cohort study design was used to assess the association of furosemide use and fractures. Both inpatients and outpatients were included in the study if they were less than 12 years old and had at least one claim with a diagnosis of CHD, cardiomyopath, or heart failure .

Many patients were diagnosed as infants, therefore, a year of previous utilization before the index date was not required, but all were required to have at least one year of follow-up data (ie, be enrolled and using services) past their medication index date (defined below). Patients were excluded if the first date for a diagnosis claim for CHD, cardiomyopathy, or heart failure occurred after the medication index date. In addition, if patients had any claims for diuretic prescriptions or ICD-9-CM codes for fractures on or before their medication index date they were also excluded from analysis. The study timeframe was described in Appendix I (available at www.jpeds.com).

Under the assumption that a patient used furosemide chronically, those who met study criteria were divided into 3 groups:

Furosemide/Adherent group: The date of the first prescription for furosemide was considered the patient's medication index date. If the patient had at least 256 days of furosemide prescriptions during the first year post-index (i.e. medication possession ratio [MPR] of 70%), they were categorized into the "Furosemide-Adherent" group. A wide range of cut-off adherence values for the MPR (63%–89%) have been used in previous adherence studies.¹⁴ However, the MPR cut-off of 70% was used for this study based on the distribution of adherence in this sample (i.e. natural break). A sensitivity analysis was conducted to validate the base model using the more commonly used 80% cut-off MPR.

Furosemide/Non-adherent group: Again, the date of the first prescription for furosemide was considered the patient's medication index date. If the patient had less than 256 days of furosemide prescriptions during the first year post-index (i.e. $MPR < 70\%$), they were categorized into the "Furosemide Non-Adherent" group.

No Furosemide group: If patients did not have a furosemide prescription at any time, but had another diuretic prescription - their index date was defined as the first date of this diuretic prescription fill. The other type of diuretics included potassium-sparing diuretics and thiazide diuretics. If patients did not have any prescriptions for diuretics, a random index date was generated from the list of medication fill dates for that patient within one year from the first prescription claim date. Patients with non-furosemide diuretics or no diuretics were combined to form the "No Furosemide" group.

Study Outcomes and Covariates

The primary outcome was the new occurrence of a bone fracture within the post-index period. In order to control for other factors that might be associated with the incidence of fractures, additional variables were included as covariates in the multivariate analyses. First, patients were divided into those who only had a CHD diagnosis and those that had either a CM and/or HF diagnosis in addition to a CHD diagnosis. Second, two diseases indicators were selected as covariates to assess comorbidity; a diagnosis of bronchopulmonary dysplasia (ICD-9-CM 770.7) and a diagnosis of low birth weight or prematurity (ICD-9-CM 764.x, 765.x). Next, clinical factors were included to adjust severity of disease: heart-related surgery (e.g. heart surgery, aortic valve repair) and utilization of proton pump inhibitors (PPIs) (i.e. omeprazole, esomeprazole, lansoprazole, rabeprazole, pantoprazole, and dexlansoprazole), which have also been shown to increase fracture risk.^{15–17} In addition, the use of less commonly utilized medications - H2-antagonist, beta-blockers, calcium or vitamin D supplementation - were added in a sensitivity analysis. These were identified only when their claims were found between the first date of diagnosis of CHD, CM, or HF and the first date of the occurrence of a fracture. For those who did not have any fractures in the study period, a random date within one year from the index date was used instead of first fracture date. In addition, other demographic factors included in the model were: age at index date; sex; and race/ethnicity (white, black, Hispanic, and others [Asian, Native Hawaiian, or uncategorized race]). The detailed ICD-9-CM codes for CHD, CM, HF, and fractures used in this study are described in Appendix II and Appendix III (available at www.jpeds.com).

Statistical Analyses

Baseline characteristics and treatment variables were compared using chi-square tests for all categorical variables and ANOVA tests for all continuous variables. Matching was performed using the propensity score matching method to reduce the bias in covariates among three groups. Propensity scores were generated using logistic regression and the matching used a greedy algorithm, which employs the nearest available pair matching methods.¹⁸ Covariates used for logistic regression included all covariates describe above; including both demographic and clinical factors. The incidence of fracture occurrence was compared among groups using chi-square tests. To estimate the odds of a fracture in the study population, a logistic regression of the matched patients, controlling for covariates was conducted. In addition, the log-rank test was used to compare survival distribution among three groups, and a Cox Proportional Hazard model with a Kaplan–Meier plot (survival curve) was used to assess time to fracture controlling for covariates. All data management and statistical analyses were completed using SAS versions 9.4 (SAS Institute Inc, Cary, NC) and Stata Statistical Software: Release 14 (StataCorp. 2015). A p-value of < 0.05 was considered statistically significant *a priori*.

Results

A total of 53,725 patients (Furosemide-Adherent: n=466, Furosemide Non-Adherent: n=2,810, No Furosemide: n=50,449) met study criteria (Appendix IV; available at www.jpeds.com). The median follow-up periods were about 3 years for each of the three

groups. Significant differences in all demographic and clinical characteristics ($p < .001$, except sex: 0.02) (Table I) were found between the unmatched groups at baseline. After propensity score matching, a final sample size of 3,912 patients (Furosemide-Adherent: $n=254$, Furosemide Non-Adherent: $n=724$, No Furosemide: $n=2,934$) was created with no differences in all baseline demographics (Table 1). The vast majority ($>91\%$) had at least two claims for CHD. Few patients had any claim for non-furosemide diuretics, such as thiazide or potassium-sparing diuretics; Furosemide-Adherent (3.9%, $n=10$), Furosemide Non-Adherent (1.5%, $n=11$), and No Furosemide group (1.7%, $n=51$).

The incidence rate of a fracture was significantly higher for the Furosemide-Adherent group compared with the both the Furosemide Non-Adherent group and the No Furosemide group for both the unmatched and matched cohorts ($p < .001$). Before matching the fracture rate was highest for the Furosemide-Adherent group (9.0%), followed by the Furosemide Non-Adherent group (5.6%), which were both higher than for patients who did not receive furosemide (3.6%). After propensity score matching, the fracture rate was still highest for the Furosemide-Adherent group (9.1%), followed by the Furosemide Non-Adherent group (7.2%), which were both higher than for patients who did not receive furosemide (5.0%). Appendix V and Appendix VI (available at www.jpeds.com) show the frequencies of the site of fractures per each group for original and matched population.

In the logistic regression model, the odds of having a fracture were 87% higher for the Furosemide-Adherent group compared with the No Furosemide group, despite controlling for covariates (OR=1.9, 95% CI=1.17–2.98, $p=0.009$, Table 2). The Furosemide Non-Adherent group also had 54% higher odds of having fractures than the No Furosemide group (OR=1.5, 95% CI=1.10–2.14, $p=0.01$). Significant covariates for fractures were age, race/ethnicity, CHD only diagnosis, and PPIs use. As each year in age increases, the odds of a fracture increased 1.2 times (OR=1.15, 95% CI=1.08–1.23, $p < 0.001$). Hispanic and black patients showed a reduced risk of fracture compared with white patients (Hispanic OR=0.6, 95% CI=0.42–0.95, $p=0.03$; black OR=0.5, 95% CI=0.24–0.99, $p=0.05$). When patients had only a CHD diagnosis, the odds of fractures were lower than patients with a comorbid diagnosis of CHD and CM or HF (OR=0.6, 95% CI=0.45–0.82, $p=0.001$). The odds ratio for PPIs users was 1.6 versus PPIs nonusers (95% CI=1.15–2.20, $p=0.005$).

Table 3 shows the results of the Cox proportional hazards regression model comparing the occurrence of fractures among cohorts including a time-to-fracture component while controlling for covariates. The proportional hazards assumption was met, meaning that the hazards ratio is a constant that does not depend on time ($p=0.42$). This model indicated that Furosemide-Adherent patients had a 56% (HR=1.6, 95% CI=1.00–2.42, $p=0.04$) increased risk of fractures consistently over 3 years, compared with furosemide nonusers. The Furosemide Non-Adherent group also had an increased risk versus the No Furosemide group, but this increase trended toward but did not reach statistical significance (HR=1.37, 95% CI=1.00–1.89, $p=0.05$). Similar to the logistic regression, significant covariates were race/ethnicity, CHD only, and PPI use. Hispanic and black patients showed a reduced risk of fracture compared with white patients (Hispanic OR=0.6, 95% CI=0.44–0.94, $p=0.02$; black OR=0.5, 95% CI=0.25–0.98, $p=0.04$). Patients with only CHD had 34% lower risk of fractures compared with patients with dual diagnoses (i.e., CHD/CM or CHD/HF) (HR=0.7,

95% CI=0.49–0.88, $p=0.004$). PPIs users had 47% higher risk of fracture than nonusers (HR=1.5, 95% CI=1.08–2.00, $p=0.02$). The log-rank test showed that furosemide users have significantly different survival distributions compared with non-users (Chi square=8.17, $p=0.02$). Furosemide-Adherent patients had a shorter time to fracture as demonstrated by Kaplan–Meier analysis (Figure).

The two sensitivity analyses using results with smaller cell sizes: using a cut-off MPR of 80%, and the addition of three covariates - H2-antagonists, beta-blocker use, and calcium or vitamin D supplementation, showed the same direction of results as the base model (Appendix VII–X; available at www.jpeds.com), and the regression analyses indicated a significant difference for furosemide-users. For the sensitivity analyses applied to the Cox proportional hazards model, again results were in the same direction, but no longer statistically different at the alpha level of 0.05 ($p = 0.08$ for MPR 80% and $p = 0.16$ when 3 new covariates were added).

Discussion

We found that patients with CHD on chronic furosemide therapy were nearly twice as likely to have a fracture compared with patients who were not on this therapy. The role of diuretics in fracture is further supported by the increased risk of fracture in those patients who had more prescription refills for a diuretic, suggesting a ‘dose-response’ type effect. Although the finding of diuretic associated fracture is well known in adult patients, this result is unique in this high-risk subset of the pediatric population.^{8,19,20} It is also unique that in our analysis, the patient population evaluated is older than previous reports demonstrating bone mineral density defects in premature neonates and infants.^{21–25} The use of furosemide in pediatric patients with CHD is common, and our findings may spur further investigation and potentially a higher clinical suspicion to evaluate for fractures.²⁶ Additionally, there were several other findings in our report which warrant discussion and evaluation from a clinical perspective.

We noted that patients with a dual diagnosis of CHD/CM or CHD/HF were at a greater risk of fracture than those patients with only CHD. Prior investigations have noted the risk of bone fracture in infants with CHD admitted to the cardiac intensive care unit, though it is unclear as to the etiology for the fractures reported.²² Vitamin D deficiency is known to be common in patients with CHD and cardiopulmonary bypass has been shown to decrease vitamin D levels in patients undergoing surgery for CHD.^{27,28} Additionally, patients who have undergone a single ventricle palliation with the Fontan procedure have demonstrated decreases in bone mineral density at a median of 10 years after the surgical procedure.²⁹ However, vitamin D has also been shown to be low in pediatric patients with heart failure and no CHD.³⁰ The lower levels of vitamin D could be a risk factor for fracture in this patient population. Overall, patients with CHD only were less likely to experience a fracture, which may be due lower doses or frequency of furosemide when compared to patients with heart failure ($p<.001$). The presence of CHD, and the underlying genotype that give rise to this phenotype, appear to influence the risk of fracture. Given these findings, vitamin D supplementation should be considered in children with CHD on chronic loop diuretic therapy.³¹

A difference in sex with regards to fracture risk was not seen, despite data suggesting that this may play a role.³⁵ white patients were at a greater risk of developing a fracture in comparison with Hispanic or black patients in our analysis. The racial/ethnic differences in bone mineral density and fracture risk are well documented.^{8,32–35} For example, it has been reported that blacks with osteoporosis have higher bone density scores as compared with white patients, which in turn is related to a lower incidence rate of fractures.³⁶ These factors should be taken into account when assessing a patient for chronic diuretic therapy.

The use of PPIs was associated with an increased risk of fracture, a finding previously reported.^{37–39} Despite this risk, they are frequently prescribed in children with heart disease.^{40–42} It is important to note that the effect of loop diuretic therapy on fracture still persisted when adjusted for PPIs use. Fractures may be able to be mitigated by decreased utilization of PPIs.^{42–44} Clinicians should be cognizant of the increased risk of fracture when using PPIs in children with CHD on chronic loop diuretic therapy and tailor use accordingly.

The limitations of this report are those that are germane to large database analyses. The current analysis only allows the reporting of an association between diuretic use and fracture incidence. We believe that a causal relationship is likely, based upon the clinical pharmacology of loop diuretics and prior literature, but cannot establish causation. There is an assumption made that patients who refilled medications were actually taking those medications, which we also cannot validate. The claims database also limited the validation of sensitivity between prescribed and filled prescription because Texas Medicaid database included only filled prescription data. Claims databases do not have the granularity to assess pertinent clinical information, such as bone mineral density values, severity of heart disease, vitamin D status, calcium/vitamin D supplementation, or fracture etiology. We were unable to quantify immobility, infection, inflammation, or dietary calcium using the claims database. However, McNally et al reported that the patients who receive a standard of care did not show additional cases of hypercalcemia or hypercalciuria.⁴⁵ We would not expect that there would be a difference in over-the-counter of calcium or vitamin D supplementation between high dose and low dose furosemide groups, or non-users group. The sensitivity analysis was conducted - controlling for calcium or vitamin D supplement - to reduce potential bias and showed the same direction with primary results. This study can serve as the basis for future investigations using robust clinical data. Next, this was a nonrandomized retrospective analysis, therefore the presence of differences in baseline patient characteristics can result in bias results. Although propensity score matching and regressions were used to account for some baseline differences, there may be unmeasured variables that can introduce bias.

Next, thiazide is known to decrease renal calcium excretion and have been associated with increased bone mineral density, resulting likely decreased the risk of fractures.⁴⁶ However, in our matched population, only 10 patients who took at least one claim for thiazide were identified in furosemide group. Moreover, because a one-time administration of thiazide would not be enough to decrease the chance of a fracture, the use of thiazides was not considered as a covariate. Sedative medications that may be related to fractures encompass a large number of medication classes and were considered too broad to be a useful covariate. Overall, despite the limitations associated with using claims data, the data presented are

similar to the results of other investigations in adults and make a compelling case for further investigations into bone health in pediatric patients with CHD who are treated with loop diuretics.

Appendix I.: Study Timeframe

a Index date: the date of the first prescription claim for furosemide or a random index date within one year from the first prescription claim date

b Fracture: the date of the first diagnosis claims for fractures after index date or a random index date within one year from the index date

Appendix II.: ICD-9-CM Code for Congenital Heart Disease, Cardiomyopathy, and Heart Failure

ICD-9-CM Code	Description
Congenital Heart Disease	
745.0	Common truncus
745.10	Complete transposition of great vessels
745.11	Double outlet right ventricle
745.12	Corrected transposition of great vessels
745.19	Other transposition of great vessels
745.2	Tetralogy of fallot
745.3	Common ventricle
745.4	Ventricular septal defect
745.5	Ostium secundum type atrial septal defect
745.60	Endocardial cushion defect, unspecified type
745.61	Ostium primum defect
745.69	Other endocardial cushion defects
745.7	Cor biloculare
745.8	Other bulbus cordis anomalies and anomalies of cardiac septal closure
745.9	Unspecified defect of septal closure

ICD-9-CM Code	Description
746.00	Congenital pulmonary valve anomaly, unspecified
746.01	Atresia of pulmonary valve, congenital
746.02	Stenosis of pulmonary valve, congenital
746.09	Other congenital anomalies of pulmonary valve
746.1	Tricuspid atresia and stenosis, congenital
746.2	Ebstein's anomaly
746.3	Congenital stenosis of aortic valve
746.4	Congenital insufficiency of aortic valve
746.5	Congenital mitral stenosis
746.6	Congenital mitral insufficiency
746.7	Hypoplastic left heart syndrome
746.81	Subaortic stenosis
746.82	Cor triatriatum
746.83	Infundibular pulmonic stenosis
746.84	Obstructive anomalies of heart, not elsewhere classified
746.85	Coronary artery anomaly
746.86	Congenital heart block
746.87	Malposition of heart and cardiac apex
746.89	Other specified congenital anomalies of heart
746.9	Unspecified congenital anomaly of heart
747.0	Patent ductus arteriosus
747.10	Coarctation of aorta (preductal) (postductal)
747.11	Interruption of aortic arch
747.20	Anomaly of aorta, unspecified
747.21	Anomalies of aortic arch
747.22	Atresia and stenosis of aorta
747.29	Other anomalies of aorta
747.31	Pulmonary artery coarctation and atresia
747.32	Pulmonary arteriovenous malformation
747.39	Other anomalies of pulmonary artery and pulmonary circulation
747.40	Anomaly of great veins, unspecified
747.41	Total anomalous pulmonary venous connection
747.42	Partial anomalous pulmonary venous connection
747.49	Other anomalies of great veins
V15.1	Personal history of surgery to heart and great vessels, presenting hazards to health
Cardiomyopathy	
425.0	Endomyocardial fibrosis
425.11	Hypertrophic obstructive cardiomyopathy
425.18	Other hypertrophic cardiomyopathy
425.2	Obscure cardiomyopathy of Africa
425.3	Endocardial fibroelastosis
425.4	Other primary cardiomyopathies

ICD-9-CM Code	Description
425.5	Alcoholic cardiomyopathy
425.7	Nutritional and metabolic cardiomyopathy
425.8	Cardiomyopathy in other diseases classified elsewhere
425.9	Secondary cardiomyopathy, unspecified
Heart Failure	
428.0	Congestive heart failure, unspecified
428.1	Left heart failure
428.20	Systolic heart failure, unspecified
428.21	Acute systolic heart failure
428.22	Chronic systolic heart failure
428.23	Acute on chronic systolic heart failure
428.30	Diastolic heart failure, unspecified
428.31	Acute diastolic heart failure
428.32	Chronic diastolic heart failure
428.33	Acute on chronic diastolic heart failure
428.40	Combined systolic and diastolic heart failure, unspecified
428.41	Acute combined systolic and diastolic heart failure
428.42	Chronic combined systolic and diastolic heart failure
428.43	Acute on chronic combined systolic and diastolic heart failure
428.9	Heart failure, unspecified

Appendix III.: ICD-9-CM Code for Fractures, Bronchopulmonary Dysplasia, and Low Birth Weight or Prematurity

ICD-9-CM Code	Description
Fractures	
733	Other disorders of bone and cartilage
767.2	Fracture of clavicle due to birth trauma
767.3	Other injuries to skeleton due to birth trauma
800	Fracture of vault of skull
801	Fracture of base of skull
802	Fracture of face bones
803	Other and unqualified skull fractures
804	Multiple fractures involving skull or face with other bones
805	Fracture of vertebral column without mention of spinal cord injury
806	Fracture of vertebral column with spinal cord injury
807	Fracture of rib(s), sternum, larynx, and trachea
808	Fracture of pelvis
809	Ill-defined fractures of bones of trunk
810	Fracture of clavicle
811	Fracture of scapula

ICD-9-CM Code	Description
812	Fracture of humerus
813	Fracture of radius and ulna
814	Fracture of carpal bone(s)
815	Fracture of metacarpal bone(s)
816	Fracture of one or more phalanges of hand
817	Multiple fractures of hand bones
818	Ill-defined fractures of upper limb
819	Multiple fractures involving both upper limbs, and upper limb with rib(s) and sternum
820	Fracture of neck of femur
821	Fracture of other and unspecified parts of femur
822	Fracture of patella
823	Fracture of tibia and fibula
824	Fracture of ankle
825	Fracture of one or more tarsal and metatarsal bones
826	Fracture of one or more phalanges of foot
827	Other, multiple, and ill-defined fractures of lower limb
828	Multiple fractures involving both lower limbs, lower with upper limb, and lower limb(s) with rib(s) and sternum
829	Fracture of unspecified bones
E887	Fracture, cause unspecified
V13.51	Pathologic fracture, Healed pathologic fracture
V13.52	Stress fracture
V15.51	Traumatic fracture, Healed traumatic fracture
V54.1	Aftercare for healing traumatic fracture
V54.2	Aftercare for healing pathologic fracture
V54.89	Aftercare for healing fracture NOS
V66.4	Following treatment of fracture
V67.4	Following treatment of healed fracture
Bronchopulmonary Dysplasia	
770.7	Chronic respiratory disease arising in the perinatal period
Low Birth Weight/Prematurity	
764.0	Light-for-dates infant without mention of fetal malnutrition
764.1	Light-for-dates infant with signs of fetal malnutrition
764.2	Fetal malnutrition without mention of light-for-dates
764.9	Fetal growth retardation unspecified
765.0	Disorders relating to extreme immaturity of infant
765.1	Disorders relating to other preterm infants
765.2	Weeks of gestation

Appendix IV.: Patient Attrition in the Texas Medicaid Database

^a Index date: the day when patients had first claims of diuretics.

^b Propensity Score matching using greedy algorithm with nearest available pair matching

Appendix V.: Site of Fractures for Original Population

	Furosemide-Adherent		Furosemide Non-Adherent		No Furosemide		TOTAL
	n	%	n	%	n	%	
Osteoporosis fracture	107	26.5 %	168	10.1%	4,418	28.2%	4,693
Fracture of radius and ulna	100	24.8%	385	23.1%	2,552	16.3%	3,037

	Furosemide-Adherent		Furosemide Non-Adherent		No Furosemide		TOTAL
	n	%	n	%	n	%	
Fracture of humerus	19	4.7%	250	15.0%	1,955	12.5%	2,224
Fracture of other and unspecified parts of femur	33	8.2%	262	15.7%	976	6.2%	1,271
Fracture of tibia and fibula	47	11.6%	43	2.6%	1,111	7.1%	1,201
Fracture of >1 phalanges of hand	4	1.0%	34	2.0%	770	4.9%	808
Fracture of clavicle	-	0.0%	62	3.7%	513	3.3%	575
Fracture of vault of skull	11	2.7%	61	3.7%	408	2.6%	480
Fracture of ankle	5	1.2%	26	1.6%	415	2.7%	446
Fracture of one or more tarsal and metatarsal bones	-	0.0%	45	2.7%	317	2.0%	362
Fracture of face bones	4	1.0%	20	1.2%	257	1.6%	281
Fracture of rib(s), sternum, larynx, and trachea	1	0.2%	30	1.8%	227	1.4%	258
Fracture of neck of femur	-	0.0%	83	5.0%	174	1.1%	257
Fracture of base of skull	30	7.4%	35	2.1%	156	1.0%	221
Fracture of clavicle	1	0.2%	6	0.4%	197	1.3%	204
Other and unqualified skull fractures	16	4.0%	17	1.0%	146	0.9%	179
Fracture of pelvis	-	0.0%	-	0.0%	177	1.1%	177
Fracture, cause unspecified	4	1.0%	16	1.0%	126	0.8%	146
Fracture of metacarpal bone(s)	-	0.0%	28	1.7%	101	0.6%	129
Fracture of unspecified bones	1	0.2%	13	0.8%	110	0.7%	124
Fracture of > 1 phalanges of foot	-	0.0%	6	0.4%	116	0.7%	122
Fracture of vertebral column without mention of spinal cord injury	15	3.7%	-	0.0%	99	0.6%	114
Traumatic fracture	-	0.0%	13	0.8%	78	0.5%	91
Fracture of carpal bone(s)	-	0.0%	14	0.8%	68	0.4%	82
Ill-defined fractures of upper limb	-	0.0%	15	0.9%	42	0.3%	57
Following treatment of healed fracture	-	0.0%	-	0.0%	42	0.3%	42
Other, multiple, and ill-defined fractures of lower limb	6	1.5%	-	0.0%	34	0.2%	40
Multiple fractures involving both lower limbs, lower with upper limb, and lower limb(s) with rib(s) and sternum	-	0.0%	32	1.9%	8	0.1%	40
Fracture of scapula	-	0.0%	-	0.0%	28	0.2%	28
Pathologic fracture	-	0.0%	1	0.1%	11	0.1%	12
Fracture of vertebral column with spinal cord injury	-	0.0%	-	0.0%	11	0.1%	11
Fracture of patella	-	0.0%	-	0.0%	8	0.1%	8
Multiple fractures involving skull or face with other bones	-	0.0%	-	0.0%	6	0.0%	6

	Furosemide-Adherent		Furosemide Non-Adherent		No Furosemide		TOTAL
	n	%	n	%	n	%	
Ill-defined fractures of bones of trunk	-	0.0%	-	0.0%	2	0.0%	2
Multiple fractures of hand bones	-	0.0%	1	0.1%	-	0.0%	1
TOTAL	404	100.0%	1,666	100.0%	15, 659	100.0%	17, 729

Appendix VI.: Site of Fractures for Matched Population

	Furosemide-Adherent		Furosemide Non-Adherent		No Furosemide		TOTAL
	n	%	n	%	n	%	
Fracture of radius and ulna	82	35.7%	182	31.2%	251	17.6%	515
Osteoporosis fracture	69	30.0%	51	8.7%	363	25.5%	483
Fracture of other and unspecified parts of femur	5	2.2%	46	7.9%	187	13.1%	238
Fracture of humerus	2	0.9%	50	8.6%	181	12.7%	233
Fracture of neck of femur	-	0.0%	77	13.2%	56	3.9%	133
Fracture of vault of skull	9	3.9%	32	5.5%	46	3.2%	87
Fracture of tibia and fibula	19	8.3%	14	2.4%	48	3.4%	81
Fracture of ankle	5	2.2%	8	1.4%	60	4.2%	73
Fracture of clavicle	-	0.0%	29	5.0%	43	3.0%	72
Fracture of >1 tarsal and metatarsal bones	-	0.0%	14	2.4%	29	2.0%	43
Other and unqualified skull fractures	16	7.0%	7	1.2%	14	1.0%	37
Fracture of metacarpal bone(s)	-	0.0%	27	4.6%	7	0.5%	34
Fracture of pelvis	-	0.0%	-	0.0%	33	2.3%	33
Fracture of >1 phalanges of hand	1	0.4%	2	0.3%	24	1.7%	27
Fracture of vertebral column without mention of spinal cord injury	15	6.5%	-	0.0%	11	0.8%	26
Fracture of rib(s), sternum, larynx, and trachea	-	0.0%	5	0.9%	21	1.5%	26
Fracture of base of skull	-	0.0%	5	0.9%	13	0.9%	18
Fracture of unspecified bones	1	0.4%	9	1.5%	8	0.6%	18
Fracture of one or more phalanges of foot	-	0.0%	6	1.0%	8	0.6%	14
Fracture, cause unspecified	4	1.7%	4	0.7%	5	0.4%	13
Fracture of face bones	-	0.0%	3	0.5%	7	0.5%	10
Traumatic fracture	-	0.0%	6	1.0%	4	0.3%	10
Fracture of carpal bone(s)	-	0.0%	2	0.3%	3	0.2%	5
Ill-defined fractures of upper limb	-	0.0%	1	0.2%	3	0.2%	4
Fracture of clavicle	-	0.0%	2	0.3%	-	0.0%	2

	Furosemide-Adherent		Furosemide Non-Adherent		No Furosemide		TOT AL
	n	%	n	%	n	%	
Other, multiple, and ill-defined fractures of lower limb	2	0.9%	-	0.0%	-	0.0%	2
Pathologic fracture	-	0.0%	1	0.2%	-	0.0%	1
Following treatment of healed fracture	-	0.0%	-	0.0%	1	0.1%	1
TOTAL	230	100.0	583	100.0%	1,426	100.0%	2,239

Appendix VII.: Sensitivity analysis: Logistic Regression of Fractures by Furosemide Use Using MPR cut-off of 80%

Variable	Category	Odds Ratio	95% CI ^a	Wald Statistic	P value ^b
Furosemide Use ^c	No Furosemide	Reference			
	Furosemide Non-Adherent	1.332	0.930–1.909	0.287	0.12
	Furosemide- Adherent	1.788	1.073–2.980	0.581	0.03
Age		1.183	1.105–1.266	0.168	<0.001
Gender	Male	Reference			
	Female	0.880	0.654–1.184	−0.128	0.40
Race/Ethnicity	White	Reference			
	Black	0.915	0.427–1.960	−0.089	0.82
	Hispanic	0.892	0.551–1.443	−0.115	0.64
	Others	0.739	0.431–1.268	−0.302	0.27
Only CHD ^d	No	Reference			
	Yes	0.646	0.465–0.898	−0.437	0.01
Bronchopulmonary dysplasia	No	Reference			
	Yes	1.211	0.801–1.829	0.191	0.36
Low birth weight / Premature	No	Reference			
	Yes	1.078	0.734–1.582	0.075	0.70
Proton Pump Inhibitor	No	Reference			
	Yes	1.875	1.314–2.676	0.629	0.001
Heart related Surgery	No	Reference			
	Yes	1.286	0.773–2.141	0.252	0.33

^aCI: confidence interval

^bSignificant at $P < 0.05$.

^cNon-adherent furosemide 70% medication possession ratio (MPR) first year after index; Adherent furosemide 70% MPR

^dYes (Only CHD) vs. No (dual diagnosis CHD/CM or CHD/CM or Only CM or Only HF or comorbidity); CHD: congenital heart disease, CM: cardiomyopathy, HF: Heart Failure

^eLikelihood Ratio Chi-Square: 64.03 ($p < 0.001$); Model Fit Statistics (Akaike information criterion): 1,498.50; Percent Concordant: 65.5%

Appendix VIII.: Sensitivity analysis: Cox Proportional Hazard Model of Fractures by Furosemide Use Using MPR cut-off of 80%

Variable	Category	Hazard Ratio	95% CI ^a	Coefficient	Pvalue ^b
Furosemide Use ^c	No Furosemide	Reference			
	Furosemide Non-Adherent	1.220	0.865–1.722	0.199	0.26
	Furosemide- Adherent	1.533	0.947–2.482	0.427	0.08
Age		1.150	1.077–1.228	0.140	<0.001
Gender	Male	Reference			
	Female	0.882	0.664–1.172	−0.125	0.39
Race/Ethnicity	White	Reference			
	Black	0.869	0.419–1.802	−0.141	0.71
	Hispanic	0.866	0.547–1.370	−0.144	0.54
	Others	0.781	0.467–1.306	−0.247	0.35
Only CHD ^d	No	Reference			
	Yes	0.692	0.506–0.946	−0.368	0.02
Bronchopulmonary dysplasia	No	Reference			
	Yes	1.175	0.794–1.739	0.161	0.42
Low birth weight / Premature	No	Reference			
	Yes	1.087	0.753–1.570	0.084	0.65
Proton Pump Inhibitor	No	Reference			
	Yes	1.728	1.234–2.418	0.547	0.001
Heart related Surgery	No	Reference			
	Yes	1.206	0.742–1.959	0.187	0.45

^aCI: confidence interval

^bSignificant at P < 0.05.

^cNon-adherent furosemide 70% medication possession ratio (MPR) first year after index; Adherent furosemide 70% MPR

^dYes (Only CHD) vs. No (dual diagnosis CHD/CM or CHD/CM or Only CM or Only HF or comorbidity); CHD: congenital heart disease, CM: cardiomyopathy, HF: Heart Failure

^eLikelihood Ratio Chi-Square: 46.55 (p<0.001); Model Fit Statistics (Akaike information criterion): 3,107.52

Appendix IX.: Sensitivity analysis: Logistic Regression of Fractures by Furosemide Use Controlling for H2-antagonist, Beta-blocker, Calcium, and Vitamin D Supplement

Variable	Category	Odds Ratio	95% CI ^a	Wald Statistic	P value ^b
Furosemide Use ^c	No Furosemide	Reference			
	Furosemide Non-Adherent	1.456	1.043–2.034	0.376	0.03
	Furosemide- Adherent	1.660	1.032–2.670	0.507	0.04
Age		1.150	1.075–1.229	0.140	<0.001
Gender	Male	Reference			

Variable	Category	Odds Ratio	95% CI ^a	Wald Statistic	P value ^b
Race/Ethnicity	Female	0.926	0.701–1.224	−0.077	0.59
	White	Reference			
	Black	0.487	0.239–0.995	−0.719	0.05
	Hispanic	0.625	0.414–0.941	−0.471	0.03
Only CHD ^d	Others	0.582	0.371–0.914	−0.541	0.02
	No	Reference			
	Yes	0.633	0.467–0.858	−0.457	0.003
Bronchopulmonary Dysplasia	No	Reference			
	Yes	1.265	0.851–1.881	0.235	0.25
Low birth weight / Premature	No	Reference			
	Yes	1.195	0.846–1.689	0.178	0.31
Proton Pump Inhibitor	No	Reference			
	Yes	1.482	1.065–2.064	0.394	0.02
Heart related Surgery	No	Reference			
	Yes	1.123	0.663–1.901	0.116	0.67
H2-antagonist	No	Reference			
	Yes	1.178	0.830–1.671	0.164	0.36
Beta-blocker	No	Reference			
	Yes	1.642	0.969–2.782	0.496	0.07
Calcium or Vitamin D	No	Reference			
	Yes	2.389	1.314–4.343	0.871	0.004

^a CI: confidence interval

^b Significant at $P < 0.05$.

^c Non-adherent furosemide 70% medication possession ratio (MPR) first year after index; Adherent furosemide 70% MPR

^d Yes (Only CHD) vs. No (dual diagnosis CHD/CM or CHD/CM or Only CM or Only HF or comorbidity); CHD: congenital heart disease, CM: cardiomyopathy, HF: Heart Failure

^e Likelihood Ratio Chi-Square: 68.97 ($p < 0.001$); Model Fit Statistics (Akaike information criterion): 1,712.67; Percent Concordant: 64.8%

Appendix X.: Sensitivity analysis: Cox Proportional Hazard Model of Fractures by Furosemide Use Controlling for H2-antagonist, Beta-blocker, Calcium, and Vitamin D Supplement

Variable	Category	Hazard Ratio	95% CI ^a	Coefficient	Pvalue ^b
Furosemide Use ^c	No Furosemide	Reference			
	Furosemide Non-Adherent	1.294	0.939–1.783	0.258	0.11
	Furosemide- Adherent	1.379	0.88–2.161	0.322	0.16
Age		1.120	1.05–1.195	0.113	0.001
Gender	Male	Reference			
	Female	0.933	0.714–1.219	−0.069	0.61
Race/Ethnicity	White	Reference			

Variable	Category	Hazard Ratio	95% CI ^a	Coefficient	Pvalue ^b
	Black	0.509	0.257–1.009	−0.675	0.05
	Hispanic	0.634	0.43–0.935	−0.456	0.02
	Others	0.665	0.433–1.02	−0.409	0.06
Only CHD ^d	No	Reference			
	Yes	0.686	0.513–0.918	−0.376	0.01
Bronchopulmonary Dysplasia	No	Reference			
	Yes	1.263	0.868–1.84	0.234	0.22
Low birth weight / Premature	No	Reference			
	Yes	1.206	0.864–1.683	0.187	0.27
Proton Pump Inhibitor	No	Reference			
	Yes	1.369	0.999–1.875	0.314	0.05
Heart related Surgery	No	Reference			
	Yes	1.049	0.635–1.732	0.048	0.85
H2-antagonist	No	Reference			
	Yes	1.198	0.859–1.671	0.181	0.29
Beta-blocker	No	Reference			
	Yes	1.679	1.027–2.745	0.518	0.04
Calcium or Vitamin D	No	Reference			
	Yes	2.338	1.365–4.005	0.849	0.002

^aCI: confidence interval

^bSignificant at P < 0.05.

^cNon-adherent furosemide 70% medication possession ratio (MPR) first year after index; Adherent furosemide 70% MPR

^dYes (Only CHD) vs. No (dual diagnosis CHD/CM or CHD/CM or Only CM or Only HF or comorbidity); CHD: congenital heart disease, CM: cardiomyopathy, HF: Heart Failure

^eLikelihood Ratio Chi-Square: 52.05 (p<0.001); Model Fit Statistics (Akaike information criterion): 3,566.42

Abbreviations:

AHFS	American Hospital Formulary Service
BMD	Bone Mineral Density
CHD	Congenital Heart Disease
CM	Cardiomyopathy
GCN	Generic Sequencing Number
HCPCS	Healthcare Common Procedure Coding System
HF	Heart Failure
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
MBD	Metabolic Bone Disease

MPR	Medication Possession Ratio
NDC	National Drug Code
PPIs	Proton Pump Inhibitors

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Figure 1.

Kaplan–Meier Curve of Risk of Fractures by Furosemide Use after 3 Years Follow-up Note: Log-rank test (Furosemide-Adherent vs. Furosemide Non-adherent: $\text{Chi}^2=0.59$, $p=0.44$; Furosemide-Adherent vs. No Furosemide: $\text{Chi}^2=5.47$, $p=0.02$; Furosemide Non-adherent vs. No Furosemide: $\text{Chi}^2=4.2$, $p=0.04$)

Table 1.

Baseline characteristics of study population

n (%)	Original Cohort ^a (n=53,725)				Propensity Score Matched Cohort ^b (n=3,912)			
	Furosemide-Adherent	Furosemide Non-Adherent	No Furosemide	P value ^c	Furosemide-Adherent	Furosemide Non-Adherent	No Furosemide	P value ^c
Total Patients	466	2,810	50,449		254	724	2,934	
Age								
Mean (SD) ^d	1.29 (2.13)	0.85 (1.70)	1.65 (1.98)	<0.001	1.67 (2.30)	1.51 (2.06)	1.58 (2.08)	0.52
0	286 (61.4)	2,008 (71.5)	20,237 (40.1)	<0.001	124 (48.8)	364 (50.3)	1,398 (47.7)	0.73
1-2	85 (18.2)	404 (14.4)	16,722 (33.2)		65 (25.6)	183 (25.3)	754 (25.7)	
3-11	95 (20.4)	398 (14.2)	13,490 (26.7)		65 (25.6)	177 (24.4)	782 (26.6)	
Gender								
Female	225 (48.3)	1,297 (46.2)	24,662 (48.9)	0.02	117 (46.1)	350 (48.3)	1,449 (49.39)	0.56
Male	241 (51.7)	1,513 (53.8)	25,787 (51.1)		137 (53.9)	374 (51.7)	1,485 (50.61)	
Race/Ethnicity								
White	45 (9.7)	315 (11.2)	5,405 (10.7)	<0.001	24 (9.5)	67 (9.2)	285 (9.7)	0.46
Black	23 (4.9)	158 (5.6)	3,757 (7.5)		18 (7.1)	38 (5.3)	138 (4.7)	
Hispanic	212 (45.5)	1,281 (45.6)	29,512 (58.5)		123 (48.4)	393 (54.3)	1,520 (51.8)	
Others	186 (39.9)	1,056 (37.6)	11,775 (23.3)		89 (35.0)	226 (31.2)	991 (33.8)	
Only CHD ^e								
No	318 (68.2)	1,490 (53.0)	2,735 (5.4)	<0.001	109 (42.9)	318 (43.9)	1,308 (44.6)	0.85
Yes	148 (31.8)	1,320 (47.0)	47,714 (94.6)		145 (57.1)	406 (56.1)	1,626 (55.4)	
Bronchopulmonary dysplasia								
No	354 (76.0)	2,449 (87.2)	46,502 (92.2)	<0.001	203 (79.9)	587 (81.1)	2,309 (78.7)	0.35
Yes	112 (24.0)	361 (12.8)	3,947 (7.8)		51 (20.1)	137 (18.9)	625 (21.3)	
Low Birth Weight/Premature								
No	242 (51.9)	1,540 (54.8)	32,062 (63.6)	<0.001	145 (57.1)	411 (56.8)	1,621 (55.3)	0.68
Yes	224 (48.1)	1,270 (45.2)	18,387 (36.4)		109 (42.9)	313 (43.2)	1,313 (44.7)	
Heart related Surgery								
No	396 (85.0)	2,328 (82.9)	50,020 (99.2)	<0.001	238 (93.7)	671 (92.7)	2,772 (94.5)	0.18
Yes	70 (15.0)	482 (17.1)	429 (0.8)		16 (6.3)	53 (7.3)	162 (5.5)	
Proton Pump Inhibitor								
No	283 (60.7)	2,083 (74.1)	46,684 (92.5)	<0.001	189 (74.4)	588 (81.2)	2,306 (78.6)	0.06
Yes	183 (39.3)	727 (25.9)	3,765 (7.5)		65 (25.6)	136 (18.8)	628 (21.4)	

^aFurosemide-Adherent: 70% medication possession ratio (MPR) first year after index, Furosemide Non-Adherent: 70% MPR^bPropensity Score matching using a greedy algorithm (nearest available pair matching methods)^cChi-square test^dAnalysis of variance (ANOVA) test

^eYes (Only CHD) vs. No (dual diagnosis CHD/CM or CHD/CM or Only CM or Only HF or comorbidity); CHD: congenital heart disease, CM: cardiomyopathy, HF: Heart Failure

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Table 2.

Logistic Regression of Fractures by Furosemide Use Controlling for Covariates

Variable	Category	Odds Ratio	95% CI ^a	Wald Statistic	Pvalue ^b
Furosemide Use ^c	No Furosemide	Reference			
	Furosemide Non-Adherent	1.537	1.104–2.139	0.430	0.01
	Furosemide- Adherent	1.868	1.172–2.977	0.625	0.009
Age		1.150	1.076–1.229	0.140	<0.001
Gender	Male	Reference			
	Female	0.934	0.707–1.234	−0.068	0.63
Race/Ethnicity	White	Reference			
	Black	0.488	0.239–0.994	−0.718	0.05
	Hispanic	0.632	0.420–0.950	−0.459	0.03
	Others	0.599	0.382–0.938	−0.513	0.03
Only CHD ^d	No	Reference			
	Yes	0.603	0.447–0.815	−0.505	0.001
Bronchopulmonary dysplasia	No	Reference			
	Yes	1.314	0.888–1.946	0.273	0.18
Low birth weight / Premature	No	Reference			
	Yes	1.190	0.843–1.679	0.174	0.32
Proton Pump Inhibitor	No	Reference			
	Yes	1.586	1.146–2.195	0.462	0.005
Heart related Surgery	No	Reference			
	Yes	1.115	0.660–1.883	0.109	0.68

^a CI: confidence interval^b Significant at P < 0.05.^c Non-adherent furosemide 70% medication possession ratio (MPR) first year after index; Adherent furosemide 70% MPR^d Yes (Only CHD) vs. No (dual diagnosis CHD/CM or CHD/CM or Only CM or Only HF or comorbidity); CHD: congenital heart disease, CM: cardiomyopathy, HF: Heart Failure^e Likelihood Ratio Chi-Square: 64.60 (p<0.001); Model Fit Statistics (Akaike information criterion): 1,672.07; Percent Concordant: 64.8%

Table 3.

Cox Proportional Hazard Model of Fractures by Furosemide Use Controlling for Covariates

Variable	Category	Odds Ratio	95% CI ^a	Wald Statistic	Pvalue ^b
Furosemide Use ^c	No Furosemide	Reference			
	Furosemide Non-Adherent	1.372	0.998–1.885	0.316	0.05
	Furosemide- Adherent	1.557	1.001–2.423	0.443	0.04
Age		1.122	1.052–1.198	0.115	<0.001
Gender	Male	Reference			
	Female	0.940	0.719–1.229	−0.062	0.65
Race/Ethnicity	White	Reference			
	Black	0.495	0.250–0.981	−0.702	0.04
	Hispanic	0.641	0.435v0.944	−0.445	0.02
	Others	0.683	0.445–1.048	−0.381	0.08
Only CHD ^d	No	Reference			
	Yes	0.657	0.492–0.875	−0.421	0.004
Bronchopulmonary dysplasia	No	Reference			
	Yes	1.292	0.890–1.877	0.257	0.18
Low birth weight / Premature	No	Reference			
	Yes	1.208	0.867–1.683	0.189	0.26
Proton Pump Inhibitor	No	Reference			
	Yes	1.469	1.078–2.002	0.385	0.02
Heart related Surgery	No	Reference			
	Yes	1.039	0.630–1.715	0.039	0.88

^aCI: confidence interval^bSignificant at P < 0.05.^cNon-adherent furosemide 70% medication possession ratio (MPR) first year after index; Adherent furosemide 70% MPR^dYes (Only CHD) vs. No (dual diagnosis CHD/CM or CHD/CM or Only CM or Only HF or comorbidity); CHD: congenital heart disease, CM: cardiomyopathy, HF: Heart Failure^eLikelihood Ratio Chi-Square: 46.90 (p<0.001); Model Fit Statistics (Akaike information criterion): 3,543.52