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An Evaluation of a Potential Calcium Channel Blocker – Lower Extremity Edema – Loop Diuretic Prescribing Cascade

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Abstract

Background/Objective: Dihydropyridine calcium channel blockers (DH-CCB) are associated with lower extremity edema (LEE). Loop diuretics have been used inappropriately to treat DH-CCB-associated LEE, constituting a prescribing cascade (PC). To identify the prevalence and factors associated with potential DH-CCB – LEE – loop diuretic PC.

Methods: The 2014 National Ambulatory Medical Care Survey was used to identify patient visits in which a DH-CCB was continued. The definition of a potential PC was the continuation or initiation of a loop diuretic in the absence of congestive heart failure, cancer, obstructive sleep apnea, chronic kidney disease or end-stage renal disease, obesity, or resistant hypertension. Multivariable logistic regression was used to identify factors related to a potential PC including demographic information, number of medications, number of patient visits in the previous 12 months, and comorbid conditions.

Results: Among the estimated 47.5 million patient visits in which a DH-CCB was continued, 4.6% had a potential PC. Visits in patients aged 65–84 years (OR 2.56, 95% CI 1.20–5.43) and 85 years (OR 3.89, 95% CI 1.76–8.61) were more likely to have potential PC compared to patients aged 18–64 years. Visits in patients with 5–7 (OR 3.75, 95% CI 1.72–8.19), 8–11 (OR 2.20, 95% CI 1.09–4.44), and 12 medications (OR 5.23, 95% CI 2.29–11.94) were more likely to have potential PC compared to patients with 0–4 medications

Conclusion: A potential DH-CCB-associated LEE loop diuretic PC was present in approximately 2.2 million patient visits in which DH-CCB was continued. Older age and an increasing number of concomitant medications were associated with this potential PC.

Keywords

Prescribing Cascade; Adverse Events; Pharmacoepidemiology; Antihypertensives

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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.

Introduction

Hypertension is the most common condition in the United States, present in one-third of adults aged 18 years or older.¹ Calcium channel blockers (CCBs) are considered a first-line option to treat hypertension in the absence of compelling comorbidities.² Dihydropyridine (DH)-CCBs are a particularly useful treatment option in older adults, as this class of medication does not require routine electrolyte monitoring or cause hypovolemia.^{3–6}

A disadvantage of DH-CCBs is the potential for lower extremity edema (LEE), which occurs in 12.3% of patients.⁵ LEE is due to increased hydrostatic pressure from precapillary arteriolar dilation which causes fluid to shift to the interstitial space and pooling of fluid in lower extremities.^{7–12} The risk of LEE due to DH-CCBs appears to be dose and duration dependent; over 25% of patients on high dose DH-CCBs for >6 months experience LEE.⁵ Although not recommended, diuretics have been used to treat DH-CCB-associated LEE.¹¹ This approach results in a prescribing cascade in which a loop diuretic is prescribed to LEE arising from an unrecognized adverse event of a DH-CCB.^{13,14} This treatment strategy should be avoided as DH-CCB-associated LEE is not the result of hypervolemia.^{7,11,12,15,16} Excessive diuresis in a euvolemic patient can lead to dehydration and consequences such as falls and increased hospitalizations.^{17–23} It is unknown how many providers are aware of this prescribing cascade; moreover, it may be increasingly difficult to identify a prescribing cascade in a patient with a complex medication list. Currently, the potential DH-CCB – LEE – loop diuretic prescribing cascade has not been described in the literature beyond a case report.²⁴

This study aims to estimate the prevalence of the potential DH-CCB – LEE – loop diuretic prescribing cascade and associated factors using a nationwide sample of ambulatory medical care visits in the United States.

Methods

Data Source

We performed a cross-sectional observational study of the publicly available National Ambulatory Medical Care Survey (NAMCS) database. The NAMCS is an annual national probability sample of patient visits to non-federally employed providers.²⁵ Medications that patients were taking prior to the visit and continued at the conclusion of the visit were classified as ‘continued.’ Medications initiated during the visit were classified as ‘new.’ The NAMCS does not include medications discontinued during the visit.

Study Population

Visits of non-pregnant patients aged 18 years or older who continued on DH-CCB (Appendix 1) were analyzed. The 2014 NAMCS dataset was selected, as it contains more detail compared to previous years.²⁶ The number of medications that could be abstracted expanded from 10 to 30 in 2014. The number of fields for diagnosis codes and reasons for visit expanded from three to five, and the number of check boxes available to identify comorbidities, regardless of diagnoses code, was expanded from 14 to 23.

Outcome Variable

We assessed new or continued use of a loop diuretic (Appendix 1) which served as a marker for a potential DH-CCB – LEE – loop diuretic prescribing cascade, henceforth referred to as PC. Individual loop diuretics were combined into one variable as these medications have the same mechanism of action. However, there are many scenarios in which concomitant use of a DH-CCB and a loop diuretic may not be a PC. Loop diuretics are used to maintain euvolemia in patients predisposed to hypervolemia, such as congestive heart failure (CHF).²⁷ Cancer, venous thromboembolism (VTE), obstructive sleep apnea (OSA), chronic kidney disease (CKD) or end-stage renal disease (ESRD), and obesity may be associated with LEE which can also lead to the prescribing of a loop diuretic.^{12,28} The use of a loop diuretic is also a treatment strategy for resistant hypertension.^{28–30} Resistant hypertension was defined as the use of a loop diuretic in visits with three or more classes of antihypertensives (Appendix 1), not including DH-CCB. Conditions that may be associated with loop diuretic use were identified based on diagnosis codes, reasons for visit, and by the statement “regardless of the diagnoses previously entered, does the patient now have <variable>, when applicable” (Appendix 2).

We assessed the percent of visits in which a loop diuretic was continued or new among visits in which a DH-CCB was continued. The outcome of potential PC was defined as a new or continued loop diuretic in the absence of CHF, cancer, VTE, OSA, CKD, ESRD, obesity, or resistant hypertension. A secondary definition of a potential PC outcome was also explored in a sensitivity analysis which included a continued or new loop diuretic in the absence of CHF. The conditions of cancer, VTE, OSA, CKD, ESRD, obesity, and resistant hypertension were removed in this secondary analysis as loop diuretic use in patient visits with these conditions may still constitute a PC (e.g., not all cancers result in LEE). We also explored the number of patient visits with potential PC coded that was coded for LEE (Appendix 2).”

Independent Variables

Older age and female sex increases the risk for DH-CCB-associated LEE, while the concomitant use of an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker may reduce this risk and may reduce the risk for this potential PC.⁵ Additional factors such as race, geographic region, and number of visits in the previous 12 months categorized in quartiles were examined. Race (e.g., White, Black or African American, Asian, Native Hawaiian or Other Pacific Islander, or American Indian or Alaska Native) was extracted from the patient chart to the NAMCS patient record. Due to low counts of Native Hawaiian or Other Pacific Islander, or American Indian or Alaska Native, these were combined with Black or African American, and race was classified as white and non-white. The number of concomitant medications, excluding DH-CCBs, loop diuretics, and potassium chloride, were classified using quartiles. Potassium chloride was not in the number of concomitant medications because it is often prescribed with loop diuretics to treat hypokalemia.³¹ Comorbid conditions were also examined as predictors for potential PC as these may be markers for increased disease burden.

Statistical Analyses

Data were analyzed using the sampling visit weights. These weights produce national estimates of the number of visits and associated characteristics.²⁵ SAS PROC SURVEYFREQ and PROC SURVEYLOGISTIC were used to account for the clustered nature of the survey.^{32,33} The DOMAIN procedure was used to ensure appropriate variance estimates.^{32,33}

The number of visits were rounded to the nearest thousand.²⁵ The percentage of visits in which a loop diuretic was used among patients who continued DH-CCBs was described along with the percentage of patients with a potential PC. Univariate analyses were used to examine factors potentially associated with a potential DH-CCB – LEE – loop diuretic PC. Weighted odds ratios (OR) and 95% confidence intervals (CI) were calculated using PROC SURVEYLOGISTIC. All variables with p-value <0.2 were included in the initial multivariable logistic regression model. Variables were removed using backward selection. Variables with greater than 30% of missingness, estimates based on fewer than 30 visits, or a relative standard error of >30% were not included in the analysis.²⁵ As this study was exploratory, no adjustments were made for multiple comparisons. This study was considered exempt by the St. Louis College of Pharmacy Institutional Review Board. All analyses were performed using SAS software version 9.4 (Cary, NC).

Results

In 2014, there were an estimated 47,526,000 visits (95% CI 46,540,000–48,514,000) in non-pregnant adults aged 18 or older in which a DH-CCB was continued. Amlodipine was the most commonly continued DH-CCB accounting for approximately 42.8 million (90.1%) visits. Appendix 3 describes patient characteristics of visits in which patients continued on a DH-CCB; 62% of visits with a DH-CCB were in adults aged 65 years or older and a loop diuretic was continued or new in 13.8% of these visits. Among patient visits in which DH-CCB was continued, 258,000 visits were coded for LEE (2.9%)

Due to estimates based on fewer than 30 visits, VTE was not included in the definition of potential PC. Potential PC was identified in 2.2 million patient visits (4.6%) using the primary PC definition of loop diuretic use in the absence of CHF, cancer, OSA, CKD or ESRD, obesity, or resistant hypertension. This translated to potential PC in 33.5% of patient visits with a new or continued loop diuretic. Potential PC was identified in 5.6 million patient visits (11.8%) in which a DH-CCB was continued using the secondary PC definition. Thus, 85.1% of patient visits with a new or continued loop diuretic met the definition for potential PC. Among patient visits with a potential PC, only 5.6% (117,000 patient visits) were coded for LEE (estimate based on fewer than 30 visits).

Race, age, diabetes, cerebrovascular disease, coronary artery disease, and number of concomitant medications were associated with the primary definition of potential PC in univariate analysis with p-value <0.2 (Table 1). The univariate analyses of the secondary definition was similar (Table 1). In multivariable analysis using the primary potential PC definition, patients aged 65–84 years (OR 2.56, 95% CI 1.20–5.43) and 85 years (OR 3.89, 95% CI 1.76–8.61) were more likely to have a potential PC compared to patients aged 18–64

years. Those with 5–7 (OR 3.75, 95% CI 1.72–8.19), 8–11 (OR 2.20, 95% CI 1.09–4.44), and 12 additional medications (OR 5.23, 95% CI 2.29–11.94) were more likely to have a potential PC compared to patients with 0–4 additional medications. Visits in non-white patients were less likely to have a potential PC compared to white patients (OR 0.47, 95% CI 0.23–0.95). Results were similar using the secondary definition (Table 2).

Discussion

Using nationally representative ambulatory visits we found that 4.6% of patient visits in which a DH-CCB was continued may have resulted in a potential PC. Up to one-third of patient visits with a new or continued loop diuretic in visits of patients who continued a DH-CCB may be a result of a PC using the primary definition of potential PC. This potential PC may have affected at least 2.2 million patient visits in 2014; however, based on the secondary definition of PC, the potential PC may be as high as 11.8% and potentially impacted up to 5.6 million patient visits. To our knowledge, this is the first study to assess the prevalence of a potential PC.

Older age was a factor associated with a potential PC. Age may be associated with an increased risk for potential PC as the risk for LEE increases with age.⁵ Another reason due to pharmacokinetic and pharmacodynamic changes associated with aging which may increase sensitivity to medications and result in a higher risk for adverse drug events.³⁴ Adverse events resulting in a PC may be misinterpreted by patients and providers as symptoms associated with aging and may not be further explored to assess if a medication may be the root cause.^{13,14}

An increasing number of concomitant medications was also associated with increased risk for potential PC. An increased number of medications may be a marker for higher comorbidity burden and patient complexity.³⁵ The number and complexity of patients that a primary care provider treats is increasing;³⁶ therefore, it may be difficult to systematically assess whether a medication may be contributing to a new symptom in an older adult. In a survey of pharmacists and student pharmacists, 98% of respondents indicated they were willing to assess for PC thus suggesting a potential role for pharmacists in mitigating PC.³⁷ One such intervention could be medication therapy management. Patients with specific type and number of comorbidities and/or medications could be eligible for medication review by a pharmacist.³⁸ If a potential DH-CCB PC is identified by the pharmacist, the probability of a medication-related problem can be assessed.³⁹ Potential DH-CCB PC may also be identified by a pharmacist through a drug utilization review in a community pharmacy or a comprehensive medication review. If the pharmacist identifies a probable PC through a medication fill history or determining by speaking with the patient that DH-CCB preceded the loop diuretic, the pharmacist can then make appropriate recommendations to the provider, such as discontinuing both the DH-CCB and loop diuretic (and potassium supplement if prescribed) and initiating a different class of antihypertensive, if necessary. Follow-up is recommended to ensure improvement or resolution of LEE symptoms and that blood pressure is being adequately controlled. Clinical decision support could also be used to assist the pharmacist in identifying potential PC.

There are several limitations to this analysis. First, our study was cross-sectional; therefore, we could not confirm temporality or assess medication utilization in prior visits. Second, the NAMCS samples patient visits and not patients; therefore, there is the potential that a patient may be counted more than once. Moreover, the NAMCS does not provide individual patient identifiers so it is not possible to identify subsequent visits by the same patient. Third, comorbidities may be under-coded in the NAMCS due to the lack of space for visit reason or available number of diagnosis codes. Fourth, there is the potential for misclassification between new versus continued medications. Specifically, ‘continued’ DH-CCB may be miscoded as ‘new’ and were excluded from analyses or ‘new’ DH-CCB may be miscoded as ‘continued’ in which there is no time for LEE to develop. Fifth, we are only able to identify potential PCs, because a true PC can only be confirmed when the potential PC medications are discontinued and symptoms resolve. Sixth, we used the use of a loop diuretic in the absence of several conditions known to be associated with LEE as part of the disease process as a surrogate for medication-associated LEE instead of coding for LEE. We used this method as ascertainment of LEE in randomized controlled trials is inconsistent and likely even more inconsistent with observational data.^{40–47} Specifically, only 5.6% of patient visits with a potential PC was coded for LEE.

There are many strengths to this study. It is the first study to estimate the prevalence of a potential PC and uses a nationwide population which expands knowledge of the PC from a single case report. Our study suggests the need to explore the PC using longitudinal data and to identify which patients may have potential PC given the presence or absence of patient characteristics and comorbidities. This would allow the development of interventions through clinical decision support to identify and mitigate PC in a clinical setting.

Conclusion

Using the 2014 NAMCS dataset, of the estimated 47.5 million patient visits in which a DH-CCB was continued 2.2 million patients visits resulted in a potential PC. This includes 33.5% of patient visits with a new or continued loop diuretic. Older age and increasing number of concomitant medications continued during patient visits were associated with potential DH-CCB–LLE– loop diuretic PC. Our study suggests the need for additional research to better identify and mitigate this PC given the large number of patients impacted by the PC.

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Appendix 1: Description of Medications

Medication Class	Level 2 Category	Level 3 Category	Drug Entry Codes (MED)	Generic Codes (DRUGID)
Angiotensin Converting-Enzyme Inhibitor	042	---	94054 (ACE INHIBITOR), 03141 (LISINAPRIL/HCTZ), 13015 (LISINAPRIL/HCTZ), 92164 (LISINAPRIL), 35224 (ZESTRIL), 92163 (ZESTORETIC), 92160 (PRINZIDE), 06017 (AMLODIPINE/BENAZEPRIL), 07170 (BENAZEPRIL/HCTZ), 92052 (LOTENSIN), 99039 (LOTENSIN/HCT), 95144 (LOTREL), 12065 (CAPTOPRIL/HCTZ), 41875 (CAPTOPRIL), 05648 (CAPOTEN), 03226 (ENALAPRI), 03328 (ENALAPRIL/HCTZ), 91074 (ENALAPRIL), 61565 (VASOTEC), 33677 (VASERETIC), 92128 (FOSINOPRIL), 08092 (MONOPRIL/HCT), 92057 (MONOPRIL), 13016 (MOEXIPRIL/HCTZ), 97018 (MOEXIPRIL), 95189 (UNIVASC), 99227 (UNIRETIC), 06106 (PERINDOPRIL), 11228 (QUINAPRIL/HCTZ), 92149 (QUINAPRIL), 92000 (ACCUPRIL), 01161 (ACCURETIC), 92150 (RAMIPRIL), 92003 (ALTACE), 97092 (TRANDOLAPRIL), 96168 (MAVIK), 97111 (TARKA)	C00042 (ANGIOTENSIN CONVERTING ENZYME INHIBITORS), d00732 (LISINOPRIL), d03266 (LISINOPRIL/HCTZ), d00730 (BENAZEPRIL), d03265 (BENAZEPRIL/HCTZ), d03829 (AMLODIPINE/BENAZEPRIL), d00006 (CAPTOPRIL), d03566 (CAPTOPRIL/HCTZ), d00013 (ENALAPRIL), d03740 (ENALAPRIL/HCTZ), d00242 (FOSINOPRIL), d00365 (MOEXIPRIL), d04141 (MOEXIPRIL/HCTZ), a70113 (PERINDOPRIL), d00365 (QUINAPRIL), d04509 (QUINAPRIL/HCTZ), d00728 (RAMIPRIL), d04008 (TRANDOLAPRIL), d04065 (TRANDOLAPRIL/VERAPAMIL)
			05197 (LOSARTAN-HCTZ), 97073 (LOSARTAN), 14011 (AZILSARTAN-CHLORTHALIDONE), 14053 (AZILSARTAN), 00133 (CANDESARTAN), 13003 (CANDESARTAN/HCTZ), 95152 (COZAAR), 95171 (HYZAAR), 11154 (EDARBI), 12200 (EDARBYCLOR), 99031 (ATACAND), 03089 (ATACAND-HCT), 00292 (TEVETEN), 13014 (IRBESARTAN-HCTZ), 01047 (IRBESARTAN), 97145 (AVAPRO), 99051 (AVALIDE), 06302 (OLMESARTAN), 11399 (OLMESARTAN-HCTZ), 13002 (OLMESARTAN-AMLODIPINE), 02013 (BENICAR), 04021 (BENICAR HCT), 10244 (TRIBENZOR), 07454 (AZOR), 06291 (TELMISARTAN), 99059 (MICARDIS), 03222 (MICARDIS-HCT), 09297 (VALSARTAN-HCTZ), 12021 (VALSARTAN-AMLODIPINE), 98141 (VALSARTAN), 97936 (DIOVAN), 99214 (DIOVAN-HCT), 07137 (EXFORGE), 09795 (EXFORGE-HCT)	d03821 (LOSARTAN), d03830 (HCTZ-LOSARTAN), d07754 (AZILSARTAN), d07818 (AZILSARTAN/CHLORTHALIDONE), d04322 (CANDESARTAN), d04711 (CANDESARTAN-HCTZ), d04266 (EPROSARTAN), d04245 (IRBESARTAN-HCTZ), d04222 (IRBESARTAN), d04801 (OLMESARTAN), d04878 (OLMESARTAN-HCTZ), d06905 (OLMESARTAN-AMLODIPINE), d07668 (OLMESARTAN-AMLODIPINE-HCTZ), d04364 (TELMISARTAN), d04737 (TELMISARTAN-HCTZ), d04113 (VALSARTAN), d04293 (VALSARTAN-HCTZ), d06662 (VALSARTAN-AMLODIPINE), d07440 (VALSARTAN-AMLODIPINE-HCTZ)
Direct Renin Inhibitors	'342'	--	11214 (ALISKIREN), 07349 (TEKTURNA), 10354 (TEKTURNA HCT), 11404 (AMTURNIDE)	d06665 (ALISKIREN), d07077 (ALISKIREN-HCTZ), d07725 (ALISKIREN-AMLODIPINE-HCTZ)
Thiazide Diuretics	--	'156'	19210 (METOLAZONE), 35155 (ZAROXOLYN), 94071 (INDAPAMIDE), 40955 (LOZOL), 04320 (CHLORTHALIDONE-ATENOLOL), 06645 (CHLORTHALIDONE), 14011 (CHLORTHALIDONE-AZILSARTAN), 15115 (HYGROTON), 30781 (TENORETIC), 12200 (EDARBYCOR), 10322 (HYDROCHLOROTHIAZIDE-TRIAMTERENE), 13003 (HYDROCHLOROTHIAZIDE-	a10585 (METHYLOTHIAZIDE-PARGYLINE), d00299 (METOLAZONE), d00260 (INDAPAMIDE), d00192 (CHLORTHALIDONE), d03258 (CHLORTHALIDONE-ATENOLOL), d07818 (CHLORTHALIDONE-AZILSARTAN), d00253 (HYDROCHLOROTHIAZIDE), d03052 (HYDROCHLOROTHIAZIDE-TRIAMTERENE), d03193

Medication Class	Level 2 Category	Level 3 Category	Drug Entry Codes (MED)	Generic Codes (DRUGID)
Loop Diuretics	--	'154'	CANDESARTAN), 14930 (HYDROCHLOROTHIAZIDE), 03141 (HCTZ-LISINAPRIL), 03328 (HCTZ-ENALAPRIL), 04022 (HCTZ-BISOPROLOL), 05197 (HCTZ-LOSARTAN), 11228 (HCTZ-QUINAPRIL), 41800 (HCTZ), 61625 (HCTZ-TRIAMTERENE), 08089 (HYDROCHLOROTHIAZIDE-METOPROLOL), 09297 (HYDROCHLOROTHIAZIDE-VALSARTAN), 11399 (HYDROCHLOROTHIAZIDE-OLMESARTAN), 12019 (HYDROCHLOROTHIAZIDE-AMILORIDE), 12065 (HYDROCHLOROTHIAZIDE-CAPTROL), 13014 (HYDROCHLOROTHIAZIDE-IRBESARTAN), 13015 (HYDROCHLOROTHIAZIDE-LISINAPRIL), 13016 (HYDROCHLOROTHIAZIDE-MOEXIPRIL), 29255 (HYDROCHLOROTHIAZIDE-SPIRONOLACTONE), 07170 (HYDROCHLOROTHIAZIDE-BENAZEPRIL), 18523 (MAXZIDE), 10815 (DYAZIDE), 19618 (MODURETIC), 00825 (ALDACTAZIDE), 08394 (LOPRESSOR HCT), 99039 (LOTENSIN HCT), 92160 (PRINZIDE), 92163 (ZESTORETIC), 33677 (VASERETIC), 94016 (ZIAC), 95171 (HYZAAR), 99227 (UNIRETIC), 99051 (AVALIDE), 99214 (DIOVAN HCT), 01161 (ACCURETIC), 03089 (ATACAND HCT), 03222 (MICARDIS HCT), 04021 (BENICAR HCT), 10354 (TEKTURNA HCT), 09795 (EXFORGE HCT), 10244 (TRIBENZOR), 11404 (AMTURNIDE), 08092 (MONOPRIL HCT), 06590 (CHLORTHAZIDE)	(HYDROCHLOROTHIAZIDE-AMILORIDE), d03247 (HYDROCHLOROTHIAZIDE-SPIRONOLACTONE), d03264 (HYDROCHLOROTHIAZIDE-METOPROLOL), d03265 (HYDROCHLOROTHIAZIDE-BENAZEPRIL), d03266 (HYDROCHLOROTHIAZIDE-LISINAPRIL), d03566 (HYDROCHLOROTHIAZIDE-CAPTROL), d03740 (HYDROCHLOROTHIAZIDE-ENALAPRIL), d03744 (HYDROCHLOROTHIAZIDE-BISOPROLOL), d03830 (HYDROCHLOROTHIAZIDE-LOSARTAN), d04141 (HYDROCHLOROTHIAZIDE-MOEXIPRIL), d04245 (HYDROCHLOROTHIAZIDE-IRBESARTAN), d04293 (HYDROCHLOROTHIAZIDE-VALSARTAN), d04509 (HYDROCHLOROTHIAZIDE-QUINAPRIL), d04711 (HYDROCHLOROTHIAZIDE-CANDESARTAN), d04737 (HYDROCHLOROTHIAZIDE-TELMSARTAN), d04878 (HYDROCHLOROTHIAZIDE-OLMESARTAN), 307077 (HYDROCHLOROTHIAZIDE-ALISKIREN), d07440 (HYDROCHLOROTHIAZIDE-AMLODIPINE-VALSARTAN), d07668 (HYDROCHLOROTHIAZIDE-AMLODIPINE-OLMESARTAN), d07725 (HYDROCHLOROTHIAZIDE-ALISKIREN-AMLODIPINE), D00190 (CHLORTHAZIDE)
	--	'154'	13118 (FUROSEMIDE), 17165 (LASIX), 96107 (BUMETANIDE), 05024 (BUMEX), 09949 (ETHACRYNIC), 10985 (EDECRIN), 97085 (TORSEMIDE), 94126 (DEMADEX),	d00070 (FUROSEMIDE), d00179 (BUMETANIDE), d00649 (ETHACRYNIC ACID), d03189 (TORSEMIDE),
Potassium Sparing Diuretics	--	'155'	12019 (AMILORIDE-HCTZ), 91002 (AMILORIDE), 19343 (MIDAMOR), 19618 (MODURETIC), 29250 (SPIRANOLACTONE), 29255 (SPIRANOLACTONE-HCTZ), 00830 (ALDACTONE), 00825 (ALDACTAZIDE), 10322 (TRIAMTERENE-HCTZ), 32273 (TRIAMTERENE), 61625 (TRIAMTERENE-HCTZ), 10865 (DYRENIUM), 10815 (DYAZIDE), 18523 (MAXZIDE), 05324 (EPLERENONE), 05269 (INSPIRA)	d00169 (AMILORIDE), d03193 (AMILORIDE-HCTZ), d00373 (SPIRANOLACTONE), d03247 (SPIRANOLACTONE-HCTZ), d00396 (TRIAMTERENE), d03052 (TRIAMTERENE-HCTZ), d04815 (EPLERENONE), a10454 (EPLERENONE-LACTOSE)
	--	--	94173 (ACEBUTOLOL), 61330 (SECTRAL), 04320 (ATENOLOL/CHLORTHALIDONE), 91063 (ATENOLOL), 30782 (TENORMIN), 30781 (TENORETIC), 00161 (BISOPROLOL), 04023 (BISOPROLOL-HCTZ), 96123 (ZIBETA), 94016	d00128 (ACEBUTOLOL), d00004 (ATENOLOL), d03258 (ATENOLOL-CHLORTHALIDONE), d00709 (BISOPROLOL), d03744 (BISOPROLOL-HCTZ), d00134 (METOPROLOL), d03264
Beta Blockers	--	--		

Medication Class	Level 2 Category	Level 3 Category	Drug Entry Codes (MED)	Generic Codes (DRUGID)
			(ZIAC), 01022 (METOPROLOL TARTRATE), 03272 (METOPROLOL SUCCINATE), 08089 (METOPROLOL-HCTZ), 19218 (METOPROLOL), 08394 (LOPRESSOR-HCT), 17885 (LOPRESSOR), 93156 (TOPROL XL), 92138 (NADOLOL), 07670 (CORGARD), 08592 (NEBIVOLOL), 08032 (BYSTOLIC), 93124 (PINDOLOL), 34263 (VISKEN), 09589 (PROPRANOLOL ER), 42985 (PROPRANOLOL), 61245 (PROPRANOLOL), 01119 (INDERAL LA), 15575 (INDERAL)	(METOPROLOL-HCTZ), d00018 (NADOLOL), d05265 (NEBIVOLOL), d00137 (PINDOLOL), d00032 (PROPRANOLOL)
Alpha/Beta Blocker	--	--	98008 (CARVEDILOL), 97142 (COREG), 08478 (COREG CR), 93203 (LABETALOL), 21373 (NORMODYNE), 31927 (TRANDATE)	d03847 (CARVEDILOL), d00016 (LABETALOL)
Dihydropyridine Calcium-Channel Blocker	--	--	93396 (AMLODIPINE), 06017 (AMLODIPINE-BENAZEPRIL), 09869 (AMLODIPINE-ATORVASTATIN), 12021 (AMLODIPINE-VALSARTAN), 13002 (AMLODIPINE-OLMESARTAN), 93189 (NORVASC), 95144 (LOTREL), 04196 (CADUET), 07137 (EXFORGE), 09895 (E-XFORGE HCT), 07454 (AZOR), 10244 (TRIBENZOR), 92125 (FELODIPINE), 09453 (FELODIPINE ER), 92073 (PLENDIL), 92132 (ISRADIPINE), 95020 (NICARDIPINE), 93036 (CARDENE), 91039 (NIFEDIPINE), 03142 (NIFEDIPINE ER), 09621 (NIFEDICAL XL), 60040 (ADALAT), 02231 (ADALAT CC), 25213 (PROCARDIA), 89067 (PROCARDIA XL), 04122 (AFEDITAB CR), 07358 (NIFEDICAC CC), 01019 (NIFEDICAL XL), 97120 (NISOLDIPINE), 96086 (SULAR)	d00689 (AMLODIPINE), d03829 (AMLODIPINE-BENAZEPRIL), d05048 (AMLODIPINE-ATORVASTATIN), d06662 (AMLODIPINE-VALSARTAN), d06905 (AMLODIPINE-OLMESARTAN), d07440 (AMLODIPINE-HCTZ-VALSARTAN), d07668 (AMLODIPINE-HCTZ-OLMESARTAN), d07725 (AMLODIPINE-ALISKIREN), d00231 (FELODIPINE), d00270 (ISRADIPINE), d00315 (NICARDIPINE), d00051 (NIFEDIPINE), d07725 (AMLODIPINE-ALISKIREN-HCTZ)
Non-Dihydropyridine Calcium-Channel Blocker	--	--	08181 (DILTIAZEM CD), 09936 (DILTIAZEM ER), 12108 (DILTIAZEM ER), 91072 (DILTIAZEM), 01094 (CARDIZEM CD), 03127 (CARDIZEM LA), 05789 (CARDIZEM), 00254 (CARTIA XT), 99210 (CARTIA), 93048 (DILACOR-XR), 96072 (TIAZAC), 00114 (DILTIA XT), 06213 (DILT-XR), 01236 (VERAPAMIL SR), 33858 (VERAPAMIL), 02244 (CALAN SR), 05347 (CALAN), 91058 (VERELAN), 03243 (VERELAN PM), 91031 (ISOPTIN SR), 40905 (ISOPTIN), 96131 (COVERA HS)	
Vasodilator	'053'	--	14840 (HYDRALAZINE), 02405 (APRESOLINE), 06102 (BIDIL), 19478 (MIDOXIDIL), 17875 (LONITEN)	d00132 (HYDRALAZINE), d05540 (HYDRALAZINE-ISOSORBIDE DINITRATE), d00135 (MINOXIDIL)
Alpha2 Agonist	--	--	89019 (CLONIDINE), 04143 (CATAPRES-TTS-1), 05895 (CATAPRES), 06044 (CATAPRES-TTS-2), 07499 (CATAPRES-TTS-3), 97089 (GUANFACINE), 30777 (TENEX)	d00044 (CLONIDINE), d00717 (GUANFACINE)
Methylidopa	--	--	19155 (METHYLDOPA), 00845 (ALDOMET)	d00133 (METHYLDOPA)

Medication Class	Level 2 Category	Level 3 Category	Drug Entry Codes (MED)	Generic Codes (DRUGID)
Potassium Chloride Supplements			24650 (POTASSIUM), 24653, 24665 (POTASSIUM CHLORIDE)	d00345 (POTASSIUM CHLORIDE)

Appendix 2: Description of Comorbidities

Variable Type	Comorbidity	Identified Using Check NAMCS Check Box	Diagnosis Codes	Reason for Visit
Primary and Secondary Definition	Congestive Heart Failure	Yes	398.91, 428.xx	--
Primary Definition	Cancer	Yes	140.0x-172.9x; 174.0x-175.9x; 196.0x-199.1x; 209.00– 209.36; 209.70–209.75; 209.79; 258.01–258.03; 789.51	2100.0
Primary Definition (no used due to low counts)	Venous Thromboembolism	Yes	453.xx	--
Primary Definition	Obstructive Sleep Apnea	Yes	327.2x	1135..5
Primary Definition	Chronic Kidney Disease	Yes (Chronic Kidney Disease)	585.x	--
Primary Definition	End-stage Renal Disease	Yes (End-stage Renal Disease)	V42.0, V45.1x, V56.x	--
Primary Definition	Obesity	Yes	278.0x, 649.1, 793.91, V85.3, V85.4, V85.54	--
Exploratory Definition	Lower Extremity Edema	No	782.3	1035.1
Covariate	Dementia		290.0x; 290.1x; 290.20; 290.21; 290.3x; 290.40; 290.41; 290.42; 290.43; 294.0x; 294.1x; 294.8x; 331.0x; 331.1x; 331.2x; 331.7x; 797.xx	--
Covariate	Diabetes	Yes	249.xx; 250.xx; 648.00– 648.04; 775.1x;	2205.0
Covariate	Chronic Lung Disease	Yes (Chronic Obstructive Pulmonary Disease or Asthma)	490.xx-492.8x; 493.xx; 494.xx; 495.0x-505.xx; 506.4x	2625.0
Covariate	Arthritis	Yes	701.0x; 710.0x-710.9x; 714.0x-714.9x; 715.xx; 716.5x; 716.6x; 716.8x; 716.9x; 718.xx; 719.0x; 719.1x; 719.4x; 719.5x; 719.9x; 720.0x-720.9x; 725.xx;	2900.0
Covariate	Cerebrovascular Disease	Yes	346.6x; 430.xx-437.xx; 438.xx	2525.0
Covariate	Coronary Artery Disease	Yes	411.xx; 412; 413.xx; 414.2x; 414.3x; 414.4x; 414.8x; 414.9x; V45.81; V45.82	2515.0
Covariate	Depression	Yes	300.4x; 301.12; 309.0x; 309.1x; 311.xx	1110.0
Covariate	Osteoporosis	Yes	733.0	--

Appendix 3: Patient Characteristics of Visits in which Patients Continued on Dihydropyridine Calcium Channel Blocker in the National Ambulatory Medical Care Survey, 2014

		Number of Visits ^a (%) (n=47,527)
Dihydropyridine Calcium Channel Blocker^b	Amlodipine	42,825 (90.1)
	Nifedipine	3,758 (7.9)
	Felodipine, Isradipine, Nicardipine, or Nisoldipine	1,012 (2.1)
Demographics	Race	38,193 (80.4)
	White	9,334 (19.6)
	Non-White	
	Sex	23,175 (48.8)
	Male	24,352 (51.2)
	Female	
	Age (years)	18,037 (38.0)
	18–64	24,992 (52.6)
	65–84	4,498 (9.5)
	85 or older	
	Region	10,615 (22.3)
	Northeast	10,215 (21.5)
	Midwest	17,272 (36.3)
	South	9,425 (19.8)
	West	
Comorbidities	Number of Visits in the Past 12 months (Quartiles)	14,674 (30.9)
	0–1	13,238 (27.9)
	2–3	10,995 (23.1)
	4–6	8,620 (18.1)
	7 or more	
	Congestive Heart Failure	1,736 (3.7)
	Cancer	5,226 (11.0)
	Venous Thromboembolism	478 (1.0)
	Obstructive Sleep apnea	3,162 (6.7)
	Chronic Kidney Disease	4,626 (9.7)
	End-stage Renal Disease	587 (1.2)
	Obesity	6,993 (14.7)
	Dementia	885 (1.9)
	Diabetes	15,706 (33.0)
Additional medications	Chronic Lung Disease	5,535 (11.6)
	Arthritis	4,532 (9.5)
	Cerebrovascular Disease	3,630 (7.6)
	Coronary Artery Disease	8,108 (17.2)
	Depression	5,425 (11.4)
	Osteoporosis	2,203 (4.6)
	Continuation of ACE Inhibitor / ARB	27,572 (58.0)
	Continued or Started Loop Diuretic	6,568 (13.8)
	Furosemide	6,090 (12.8)
	Bumetanide, Torsemide, Ethacrynic Acid ^d	484 (1.0)
	Continuation of 3 or more Blood Pressure Lowering Medications ^c	6,399 (13.5)
	Number of Medications Continued (Quartiles) ^c	14,540 (30.6)
	0–4	13,702 (28.8)
	5–7	11,113 (23.4)

	Number of Visits ^a (%) (n=47,527)
8–11	8,172 (17.2)
12 or more	

^a = x 10³

^b = May be on more than type of Dihydropyridine Calcium Channel Blocker

^c = Not including Dihydropyridine Calcium Channel Blocker, Loop Diuretic, or Potassium Chloride

^d = Bumetanide, Torsemide, Ethacrynic Acid combined due to raw counts <30 for individual medications

ACE = angiotensin converting enzyme; ARB = angiotensin 2 receptor blocker

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Table 1:

Factors Associated with Dihydropyridine Calcium Channel Blocker – Lower Extremity Edema – Loop Diuretic Prescribing Cascade – Univariate Analyses

	Primary Definition		Secondary Definition	
	Loop Diuretic in the Absence of CHF, cancer, OSA, CKD or ESRD, obesity, or resistant hypertension	P-Value	Loop Diuretic in the Absence of CHF	P-Value
Demographics				
Race				
White	1.00 (reference)	0.007	1.00 (reference)	0.014
Non-White	0.38 (0.19–0.76)		0.55 (0.35–0.89)	
Age				
18–64	1.00 (reference)	<0.001	1.00 (reference)	0.0009
65–84	3.10 (1.44–6.69)		2.08 (1.27–3.42)	
85 or older	4.92 (2.26–10.71)		2.60 (1.46–4.60)	
Number of Visits in the Past 12 months (Quartiles)		0.069		0.619
0	1.00 (reference)		1.00 (reference)	
1–2	2.92 (1.32–6.44)		1.45 (0.71–2.98)	
3–5	2.57 (1.15–5.72)		1.48 (0.79–2.74)	
6 or more	1.71 (0.79–3.74)		1.15 (0.59–2.26)	
Comorbidities^b		0.107		<0.001
Diabetes	1.48 (0.92–2.38)		2.33 (1.64–3.32)	
Chronic Lung Disease	1.10 (0.40–3.03)	0.851	1.59 (0.88–2.87)	0.125
Cerebrovascular Disease	2.44 (0.93–6.37)	0.069	1.96 (0.65–5.98)	0.235
Coronary Artery Disease	3.36 (1.28–8.82)	0.014	3.11 (1.53–6.29)	0.002
Medications		<0.001		<0.001
Number of Medications (Quartiles) ^{a,b}				
0–4	1.00 (reference)		1.00 (reference)	
5–7	4.39 (1.98–9.74)		3.81 (2.11–6.90)	
8–11	2.69 (1.35–5.34)		5.11 (2.88–9.07)	
12 or more	6.68 (2.89–15.42)		9.57 (5.26–17.41)	

^a = Continued on specified medication

^b = Does not include Dihydropyridine Calcium Channel Blocker, Loop Diuretic, or Potassium Chloride

Demographics (Sex, Region); Comorbidities (Arthritis, Depression); Medications (Angiotensin converting enzyme/Angiotensin 2 receptor blocker) were not included in Table as these variables had p-value 0.2; Demographics (Race – Other) Comorbidities (Dementia, Osteoporosis) were not assessed as potential confounders due to estimates based on <30 raw visits

CHF = congestive heart failure; CI = confidence interval; CKD = Chronic Kidney Disease, ESRD = end-stage renal disease; OR = odds ratio; OSA = obstructive sleep apnea

Table 2:

Factors Associated with Dihydropyridine Calcium Channel Blocker – Lower Extremity Edema – Loop Diuretic Prescribing Cascade – Multivariable Analyses

Primary Definition		Secondary Definition
Loop Diuretic in the Absence of CHF, cancer, OSA, CKD or ESRD, obesity, or resistant hypertension ^a		Loop Diuretic in the Absence of CHF ^b
Odds ratio (95% Confidence Interval)		
Demographics	Age	
	18–64	1.00 (reference)
	65–84	2.56 (1.20–5.43)
	85 or older	3.89 (1.76–8.61)
	Race	
	White	1.00 (reference)
	Non-White	0.47 (0.23–0.95)
Comorbidities	Diabetes	--
Medications	Number of Medications (Quartiles) ^{c,d}	
	0–4	1.00 (reference)
	5–7	3.75 (1.72–8.19)
	8–11	2.20 (1.09–4.44)
	12 or more	5.23 (2.29–11.94)
		1.69 (1.16–2.46)
		1.00 (reference)
		3.25 (1.78–5.94)
		4.04 (2.27–7.20)
		6.91 (3.73–12.77)

^a = Diabetes, cerebrovascular disease, coronary artery disease removed from model using backward selection

^b = Cerebrovascular disease, diabetes, use of angiotensin converting enzyme inhibitor or angiotensin 2 receptor blocker, coronary artery disease, race removed from model using backward selection

^c = Continued on specified medication

^d = Does not include Dihydropyridine Calcium Channel Blocker, Loop Diuretic, or Potassium Chloride