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Trends of antihypertensive use among patients with cancer and hypertension in the United States 2002–2019☆

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ABSTRACT

Background: Hypertension (HTN) is the most frequently reported comorbidity in patients with malignancy. This study was conducted to assess the trend of different antihypertensive (AHT) medications used in cancer patients.
Methods: We used the Medical Expenditure Panel Survey (MEPS) database from 2002 to 2019 to identify adult (age >18 years) cancer patients with HTN using appropriate International Classification of Disease (ICD)-9 and ICD-10 codes. Benign and uncertain neoplasms were excluded. *P*-trend values were calculated using weighted logistic regression with "year" as the predictor variable.
Results: We identified ~46 million adult hypertensive cancer patients with an increasing trend from 2002 to 2019 (3.3 m–6.7 m). Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB) use in hypertensive cancer patients increased steadily, while diuretics and combined drugs decreased. Calcium channel blocker (CCB) use increased since 2014–15. In cancer patients with heart failure (HF), beta-blocker (BB) use increased; however, diuretic use peaked in 2014–15 and declined. The use of ACEi/ARB in cancer patients with Diabetes (DM) has increased, whereas BB, CCB, and diuretic use remained stable. Hypertensive cancer patients with Atherosclerotic Cardiovascular Disease (ASCVD) had increased ACEI/ARB use. Combination AHT use has decreased broadly.
Conclusion: The ACEI/ARB and CCB use trends increased over the past two decades, whereas diuretics have declined. In cancer patients with DM or ASCVD, the use of ACEI/ARB is trending up. BB use showed an increasing trend in patients with HF. Combined AHT and diuretics use decreased. Total expenditure and out-of-pocket expenditure have a decreasing trend for all AHT medications.

Credit author statement

Harshith Thyagaturu MD:Investigation, Analysis, Data Curation; Bandar Alyami MD: Writing, Analysis; Nicholas Roma MD: Data Curation, Writing; Karthik Gonuguntla MD: Writing, Resources; Gayatri Bondi: Writing, Resources; Brijesh Patel, DO: Supervision.

1. Introduction

Cardiovascular disease and cancer are the leading causes of morbidity and mortality worldwide. Hypertension (HTN) is one of the most frequently reported medical issues in patients with malignancy and is considered a significant risk factor for the development of cardiovascular disease (CVD) [1,2]. Advances in cancer therapies have led to an improved prognosis and survival of cancer patients. Consequently, cardiovascular disease has been reported as the leading cause of late morbidity and mortality in cancer survivors [3]. A recent study expected more than 22 million cancer survivors in the United States by 2023 [4]. Another retrospective study published by Fraeman et al. found up to a 3.5-fold increase in the risk for the development of new-onset HTN after the initiation of chemotherapy [5].

The complex relationship and interaction between cancer, anti-cancer therapies, and hypertension have led to the development of a new subspecialty, onco-hypertension. Limited literature describes the

Table 1

Baseline characteristics and trends of cancer patients with concomitant diagnosis of hypertension: Analysis of MEPS dataset 2002–2019.

Year	2002–03	2004–05	2006–07	2008–09	2010–11	2012–13	2014–15	2016–17	2018–19	P-trend
Total adults with cancer	4,035,312	7,643,148	9,391,898	10,195,588	12,720,916	8,052,919	5,296,115	9,413,456	13,419,063	<0.01
Total adults with cancer and hypertension	1,651,604	3,400,968	4,565,708	6,115,125	7,437,819	4,659,041	4,062,934	5,431,066	6,778,299	<0.01
Female (%)	49.9	49.1	50.7	47.7	50.4	49.1	40.4	46.9	48.4	0.61
Mean age (SD)	68.5	70.3	69.1	68.9	68.6	68.8	69.9	70.5	70.9	<0.01
Age categories (%)										
18–49 yrs	5.9	4.6	5.5	5.6	5.2	5.5	4.1	4.4	4	0.24
50–64	27.8	22.4	28.6	25.2	29.8	27.1	24	19.8	20.1	0.02
65–74	34.2	33.2	28.9	34.6	32.2	34.9	30.8	34.7	35.1	0.37
>75	32	39.7	36.9	34.6	32.7	32.4	41	40.9	40.8	0.37
Regions (%)										
Northeast	21.2	21	17.1	24.2	19.7	20.6	20.3	22.3	23	0.43
Midwest	22.2	24.2	25.6	24.4	22.8	22.6	25.3	21.5	18.4	0.07
South	39.2	34	37.4	34	41.1	42.2	36.5	39.2	39.2	0.32
West	17.3	20.7	19.9	17.3	16.4	14.5	17.7	16.8	19.3	0.79
Race (%)										
White	86.2	84.8	76.4	79.1	80.9	81.7	81.7	77.2	77.6	0.02
Black	8.2	7.3	12.6	10.9	10.9	9.6	9.7	12.6	11.2	0.13
Hispanic	2.9	4.4	5.6	5.3	5.6	5.3	4.7	6	6.8	0.02
Asian or Pacific Islander	1.8	2.1	2.3	2.3	1.8	2.4	1.8	2	1.4	0.48
Native American	0.3	0.5	0.1	0.5	<0.5	0.4	0.3	1	1.3	0.12
Multiple races reported	0.5	0.7	2.8	1.8	0.5	0.5	1.6	1	1.6	0.99
Family income (%)										
Poor/Negative (</= poverty line)	9.7	9.1	7.3	8.5	9.3	10.4	11.5	12.3	11.3	0.02
Near Poor (Up to 125% of the poverty line)	5.7	7.3	6.8	7.8	5.4	8.4	5.8	6.7	4.8	0.33
Low income (125–200% of the poverty line)	16.4	16.2	17.9	15.4	16.2	18.8	18.8	14.9	13.4	0.16
Middle income (200–400% of the poverty line)	29.5	28.5	27.2	30.9	30.2	27.9	20.4	23.9	23.2	0.01
High income (>400% of the poverty line)	38.6	38.8	40.7	37.3	38.7	34.4	43.4	42.1	47.2	0.02
Insurance coverage (%)										
Public insurance (Medicare/Medicaid) (%)	71.2	66.5	62.3	58	64.4	61.8	60.2	59.3	55	<0.01
Any Private insurance (%)	27.6	31.1	34.9	39.8	32.5	35.8	38.4	39.8	43.9	<0.01
Uninsured (%)	1.1	2.4	2.6	2.2	3.1	2.3	1.2	0.8	1.1	0.13
Charlson comorbidity index (CCI) score (mean)	2.3	2.3	2.4	2.6	2.6	2.5	2.6	2.8	2.5	<0.01
Charlson comorbidity score (%)										
Score 0	7.4	8.6	5.5	0	0.5	0	0	0	0	<0.01
Score 1	1.9	3.6	1.3	0.4	0.2	0	0	0	0	<0.01
Score 2	65.6	61.3	60.1	60.7	61	59.9	58.3	54.2	64.9	0.63
Score ≥3	25.1	26.4	33.1	38.9	38.3	40.1	41.7	45.7	35.1	<0.01
Comorbidities (%)										
Heart failure	4.5	7.2	4.5	3.7	3.8	2.7	10.6	6.1	1.9	0.06
Diabetes mellitus	16.1	21.7	27.1	29.5	30.2	33.5	37.1	29	24.1	0.05
ASCVD	15.3	11.3	21.5	34.5	29.9	33.2	36.5	24.2	20.1	0.14
Different cancers (n)										
Gastrointestinal	231,091	481,167	671,905	634,066	841,355	498,499	283,983	385,772	398,702	<0.01
Breast	353,046	696,334	1,026,102	1,439,572	1,830,147	672,514	716,942	1,003,116	1,505,020	0.51
Lung	100,230	261,458	308,501	351,641	603,029	380,309	446,925	622,335	464,528	0.14
Genitourinary	604,842	1,042,831	1,722,889	2,841,167	2,939,363	1,777,720	1,484,616	2,683,172	2,431,964	0.18
Hematological	132,388	344,339	444,552	633,948	759,354	579,196	681,114	701,282	602,513	0.41

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; ASCVD = atherosclerotic cardiovascular disease.

prevalence of various antihypertensive (AHT) use in cancer patients. To bridge this knowledge gap, we aimed to describe the trends in using different AHT medications among cancer patients in the United States (US).

2. Methods

The Medical Expenditure Panel Survey (MEPS) database is a nationally representative large-scale survey of non-institutionalized US civilians, their medical providers, pharmacies, and employers to collect data on specific health services as well as the cost of healthcare use. The MEPS database began in 1996 and is sponsored by the Agency for Healthcare Research and Quality (AHRQ). The population for MEPS was derived from a sample of families and individuals across the US who

were the subsample that participated in the previous year's National Health Interview Survey (NHIS). The participants were interviewed over the telephone and asked a series of questions over a period of two years. The responses were collected and coded into the dataset. During the interview, the respondents were asked about medications they or family members purchased or otherwise obtained during that period. With written permission from the participants, the pharmacies were contacted to obtain a computer-generated profile of the medication name, national drug code, dose, quantity, the amount paid, and the source of payment for each prescription. For each drug, the dollar amount, along with out-of-pocket (OOP) expenditure, was reported.

We downloaded the 2002 to 2019 MEPS data files from the official MEPS website [6]. We identified adult (age ≥18 years) cancer patients with HTN using the appropriate International Classification of Diseases

Table 2
Trends of Anti-Hypertensives use and their Expenditure in Cancer Patients with Hypertension: Analysis of MEPS Dataset 2002 to 2019.

Year	2002–03	2004–05	2006–07	2008–09	2010–11	2012–13	2014–15	2016–17	2018–19	*P*-trend
Total adults with cancer and hypertension	1,651,604	3,400,968	4,565,708	6,115,125	7,437,819	4,659,041	4,062,934	5,431,066	6,778,299	<0.01
Anti-Hypertensives (%)										
ACEI/ARB	42.9	46.2	43.6	48.4	48.2	52.4	58.3	54.9	58.8	<0.01
Beta-blockers	34.8	44.2	39.7	39.2	38.3	40.6	41.8	40.4	39.8	0.73
Calcium channel blockers	26.1	28.2	17.8	21.4	20.2	22.9	21.9	31.2	29.2	<0.01
Diuretics	37.5	36.7	36.7	35.7	33.2	35.2	32.5	28.8	27.8	<0.01
Combination drugs	21.2	24.1	27.2	26.2	21.7	23.1	16.4	12.6	14.3	<0.01
Clonidine	3.3	2.9	3.7	0.9	2.4	2.8	3.7	2.2	2.3	0.41
Hydralazine	0	0.5	0.6	0.6	1.8	2.5	2.7	2.1	3.9	<0.01
Total expenditure (mean/person-years) (USD)										
ACEI/ARB	221.1	223	168	167	101.3	167	101	112	79.5	<0.01
Beta-blockers	130.4	159	122	72	55.2	78.4	76.4	63.5	45.2	<0.01
Calcium channel blockers	147.7	142	72.3	70	44.3	33.6	26.4	48.2	45.6	<0.01
Diuretics	42.6	39.3	29.5	23.1	17.9	15.6	19.8	26.5	17.7	0.09
Combination drugs	79.5	103	103	122	90.9	84.5	66.5	29.7	35.6	<0.01
OOP expenditure (mean/person-years) (USD)										
ACEI/ARB	112.1	99.5	58.1	43.3	33.9	33	21.2	18.8	16.9	<0.01
Beta-blockers	71.1	77.4	48.3	23.8	20.3	22.4	18.7	15.9	13.2	<0.01
Calcium channel blockers	63.6	56.0	27.1	21.4	10.4	11	9.3	8.7	8.4	<0.01
Diuretics	24.7	24.4	14.1	11.6	10.9	8.7	8.5	6.6	5.1	<0.01
Combination drugs	57.2	59.0	41.9	40.6	26.3	18.1	12.6	8.1	6.6	<0.01
Total prescription expenditure (In millions, USD)										
ACEI/ARB	518.6	758	768	1028	754	778	413	609	539	<0.01
Beta-blockers	215.9	542	556	440	412	365	322	345	307	<0.01
Calcium channel blockers	244.3	482	331	429	331	159	94.1	262	310	<0.01
Diuretics	71	134	135	142	134	72.8	88.6	144	121	0.09
Combination drugs	132	350	470	746	675	394	250	161	241	<0.01
Total OOP prescription expenditure (In millions, USD)										
ACEI/ARB	184.6	339	265	265	252	155	73.3	102	115	<0.01
Beta-blockers	116.4	263	220	147	151	104	69	86.2	89	<0.01
Calcium channel blockers	105.1	190	124	131	77.4	50.4	32.8	47.9	57.3	<0.01
Diuretics	39.7	82.4	64.9	70.9	80.9	40.3	28.5	35.1	34.8	<0.01
Combination drugs	93.7	201	192	248	196	83.9	47	43.6	44	<0.01

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; OOP = out-of-pocket.
All reported monetary values have been adjusted to constant 2019 US dollars using the Consumer Price Index (CPI) inflation calculator from the US Bureau of Labor Statistics.

Ninth and Tenth Revision-Clinical Modification (ICD-9-CM and ICD-10-CM codes: see Supplementary Table S1). Patients with benign and unspecified cancers were excluded from the study. We pooled two consecutive years of data together to easily analyze and avoid duplication. The prevalence of different classes of AHT use like angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEi/ARB), beta-blockers (BB), calcium channel blockers (CCB), diuretics, and combination drugs in cancer patients and various comorbidities was extracted from the database. Combined alpha and beta blockers like labetalol and carvedilol are classified under "beta-blockers", and Mineralocorticoid-antagonists are classified under diuretics in the database. In addition, we also explored AHT use in 4 different groups: all patients, HF patients, diabetes mellitus (DM) patients, and atherosclerotic cardiovascular disease (ASCVD) patients. The comorbidities were identified based on the ICD-9-CM and ICD-10-CM codes described in Supplementary Table S1. For the trend analysis, we combined the 2002–2019 dataset to create a mega file and used the weighted logistic regression "year" as the predictor variable. All reported monetary values were adjusted to constant 2019 US dollars using the Consumer Price Index (CPI) inflation calculator from the US Bureau of Labor Statistics for the expenditure analysis. All p-trend values were calculated based on 2-tailed tests, with 0.05 as a threshold for statistical significance and adjusted for baseline demographics and comorbidity differences. All statistical analyses were performed using the Stata software package, version 17.0 SE-Standard Edition (StataCorp, 4905 Lakeway Drive, College Station, TX). Stata accounted for the complex survey sampling design of the MEPS using the available person weights and variance estimates to calculate national-level totals, means, and proportions.

3. Results

We identified a total of ~46 million adult hypertensive cancer patients with an increasing trend in newly diagnosed hypertensive cancer patients from 2002 to 2019 (3.3 million to 6.7 million) with a mean age of 69.5 ± 0.9 years and a predominantly White population (80.6%), followed by African-Americans (10.3%) and Hispanics (5.1%). The baseline characteristics, demographics, and trends across the study period are reported in Table 1.

Two-thirds of our study cohort had incomes above 200% of the poverty line. Even though there was an absolute proportional increase, there was no statistically significant difference in the trend of burden for comorbidities like heart failure (HF), DM, and ASCVD. Genitourinary cancers, including prostate, were the most commonly reported cancers (30–50%), followed by breast and gastrointestinal (GI) cancers. The prevalence of GI cancers trended down (p < 0.01) over the study period, while the genitourinary and breast cancer prevalence remained steady during the analysis period. The ACEi/ARB use in hypertensive cancer patients increased steadily from 42.9% in 2002–2003 to 58.8% in 2018–19 (p < 0.01) (Table 2 and Figure-1A). The diuretics (37.5%–27.8%; p < 0.01) and combination AHT use (21.2%–14.3%; p < 0.01) has trended down from 2002 to 2003 to 2018–2019, while CCB use has picked up since 2014–15.

In hypertensive cancer patients with HF, BB use has increased (47.1%–87.9%; p = 0.02) (Table 3 and Figure-1B). However, diuretic use peaked in 2014–15 (94.5%) and has since declined (45.1% in 2018–19). In hypertensive cancer patients with DM, ACEI/ARB use has increased (50.3–71.5%; p < 0.01), whereas BB, CCB, and diuretic use remained stable over the years (Figure-1C). Hypertensive cancer
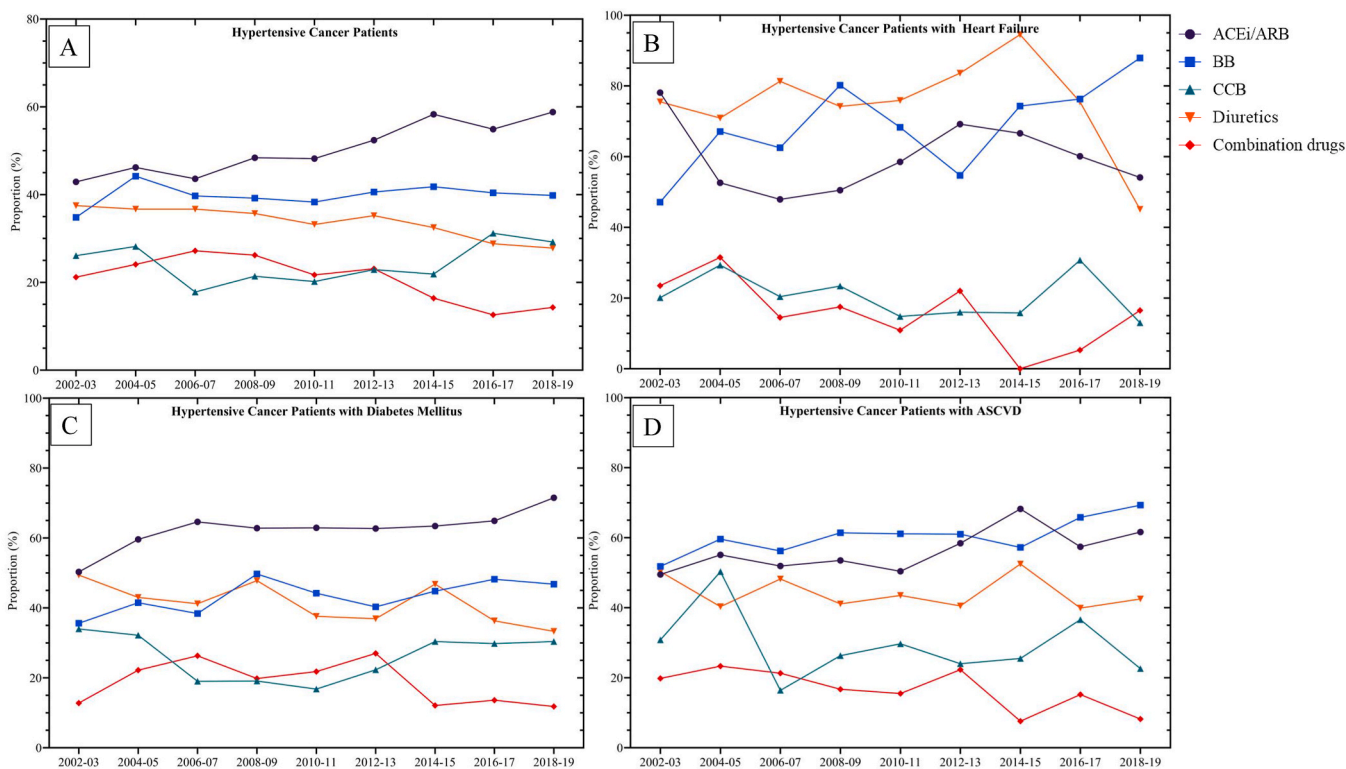
Fig. 1. A: Nationwide trends in antihypertensive use in cancer patients from 2002 to 2019
Figure -1B Trends in antihypertensive use in cancer patients with heart failure
Figure-1C Trends in antihypertensive use in cancer patients with diabetes mellitus
Figure-1D Trends in antihypertensive use in cancer patients with ASCVD.

Table 3
Categorization of cancer patients with hypertension by status of heart failure, diabetes mellitus and atherosclerotic cardiovascular disease.

Ca + HTN patients with Heart Failure (%)	2002–03	2004–05	2006–07	2008–09	2010–11	2012–13	2014–15	2016–17	2018–19	P-trend
ACEI/ARB	78.1	52.6	47.9	50.5	58.5	69.2	66.6	60.1	54.1	0.1
Beta-blockers	47.1	67.1	62.5	80.2	68.3	54.7	74.3	76.3	87.9	0.02
Calcium channel blockers	20.1	29.3	20.4	23.4	14.8	16	15.8	30.7	13	0.89
Diuretics	75.5	70.9	81.3	74.2	75.9	83.6	94.5	75.5	45.1	0.47
Combination drugs	23.5	31.5	14.5	17.5	10.9	22	0	5.3	16.5	0.02
Ca + HTN patients with Diabetes Mellitus (%)										
ACEI/ARB	50.3	59.6	64.6	62.8	62.9	62.7	63.4	64.9	71.5	0.07
Beta-blockers	35.6	41.5	38.4	49.7	44.2	40.3	44.8	48.2	46.8	0.25
Calcium channel blockers	34	32.2	19.02	19.1	16.8	22.3	30.4	29.8	30.4	0.25
Diuretics	49.4	43	41.2	47.8	37.6	36.9	46.8	36.3	33.3	0.01
Combination drugs	12.8	22.2	26.3	19.8	21.8	27	12.1	13.6	11.8	0.03
Ca + HTN patients with ASCVD (%)										
ACEI/ARB	49.5	55.1	51.9	53.5	50.4	58.4	68.2	57.4	61.6	<0.01
Beta-blockers	51.8	59.6	56.2	61.4	61.1	61	57.2	65.8	69.3	0.14
Calcium channel blockers	30.8	50.3	16.4	26.3	29.7	24	25.5	36.6	22.6	0.82
Diuretics	50.3	40.3	48.2	41.1	43.5	40.5	52.5	39.9	42.5	0.44
Combination drugs	19.8	23.3	21.3	16.7	15.5	22.3	7.6	15.2	8.2	0.01

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; ASCVD = atherosclerotic cardiovascular disease; Ca = cancer; HTN = hypertension.

patients with ASCVD had an increasing trend of ACEI/ARB use from 2002 to 03 to 2018–19 (49.5% vs. 61.6%, p < 0.01) (Figure-1D). There was no statistically significant difference in trends of BB, CCB, and diuretic use in the ASCVD group. Combination AHT use has decreased significantly in all categories, including HF, DM, and ASCVD patients. The total expenditure for ACEi/ARB decreased (221.1–79.5, p < 0.01) (Table 2). Out-of-pocket (OOP) expenditure in ACEi/ARB decreased (112.1–16.9, p < 0.01). Both mean total, and OOP expenditure had a decreasing trend in all AHT medications across this study.

4. Discussion

In this nationally representative contemporary MEPS-based analysis of adult hypertensive cancer patients, ACEI/ARB and CCB use increased over the past two decades. The use of diuretics has declined. In hypertensive cancer patients with DM or ASCVD, the use of ACEI/ARB is trending up. In patients with HF, BB use showed an increasing trend. Combination AHT medications and diuretics have been used less commonly over recent years. In addition, the total and OOP expenditure for all AHT agents is decreasing over the years.

HTN, DM, Coronary Artery Disease (CAD), and HF are common

coexisting comorbidities, with the prevalence of HTN doubled in diabetic patients compared to the general population [7]. In addition, HTN and DM are well-known risk factors for the development of ASCVD and CAD, which can eventually lead to ischemic cardiomyopathy and, subsequently, HF [7]. Cancer patients have a greater chance of developing these comorbidities, so selecting the ideal AHT medication should be considered carefully. Our study results are analogous to the findings of other nationally representative studies, albeit performed in all adult hypertensive patients. A 2001 to 2010 study by Gu et al. showed increasing use of ACEI/ARB and CCB in the adult hypertensive population, which is in conjunction with ACC/AHA's recommended first-line AHT agent [8,9]. The ACEI/ARB's many advantages could explain it's increasing trend. ACEI/ARB slows the progression of diabetic nephropathy and improves mortality in HF patients [10,11]. In addition, ACEI, such as enalapril, has some protective effects in patients receiving high-dose chemotherapy [12]. Although there is little evidence of which AHT to select in this population, currently, ACEI/ARBs seem to have the best risk-to-reward ratio. BBs are not recommended as first-line treatment for hypertension; however, they can be used in the presence of HF, CAD, or both, given that they have proven mortality benefits and AHT effects [13,14]. The trend in CCB use increased over the study period. The medication is one of the recommended first-line therapies for HTN according to the ACC's recent guidelines and additionally was found to be one of the most frequently prescribed medications in the United States [15,16]. Decreased diuretic use in cancer patients could be ascribed to frequent electrolyte and acid-base disturbances that complicate the management of cancer patients. Additionally, the introduction of Sodium-Glucose Transporter-2 (SGLT-2) inhibitors could have also contributed to decreased diuretics usage. Combination AHT medications are reported to be more effective than monotherapy agents in the early course of treatment; however, randomized clinical trials found that patients started on monotherapy eventually achieved blood pressure control as patients did with combination therapy [17]. We found decreased combined AHT use in cancer patients at a higher risk of autonomic dysfunction and orthostatic hypotension.

Our study is not without limitations. First, MEPS was conducted in a non-institutional adult population; hence, the results are only generalizable to community adults. Second, our classification of adults into different comorbidities relied on self-report, which could underestimate our risk groups' sizes. Additionally, targeted molecular therapies have increased, such as VEGF-1 inhibitors that will naturally grow a patient's blood pressure [18]. Further research can include taking into account these therapies and their individual effects on hypertensive treatment. However, our study has its own strength by using MEPS, which collects data from different sources, including providers, employers, and individuals on a broad spectrum of healthcare issues by using multiple parameters. This nationally representative study observed an increased ACEI/ARB use in cancer patients with HTN and in those with other comorbidities such as DM and ASCVD risk. BB use was trending up in the HF group. Combined AHT drugs with diuretics were used less commonly during our study period. Future studies are required to assess AHT medications use in cancer patients as well as a direct comparison to AHT use in patients without cancer.

5. Conclusion

In conclusion, our study demonstrates that in adult hypertensive cancer patients, the widespread use of ACEI/ARBs and CCBs is increasing while diuretics and combination AHT are decreasing. Consistent with the guidelines, patients with DM had increasing use of ACEI/ARB; in HF patients, the use of BB increased. In addition, the total and OOP prescription costs for all the major AHT medications are in decreasing trend over the years. Further research on contemporary trends of AHT use in specific cancer patient populations is needed.

Declaration of competing interest

No conflict of interests exist.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcrp.2023.200196.

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