Trends in the Utilization of and Expenditures on Mortality-Lowering Drugs in US Adults With Heart Failure

Exploring the Medical Expenditure Panel Survey

Pritpal Araich, MS4

Introduction

Heart failure is a clinical syndrome in which the heart is unable to generate enough output to meet the metabolic needs of peripheral tissues. It holds an unfortunate distinction of being both common and deadly. Over 6 million US adults have a current diagnosis of heart failure, over 500,000 new cases are diagnosed every year, it is the leading cause of hospitalizations in the Medicare population, and almost half of heart failure patients have an average life expectancy of only 5 years.[1,2] Much effort has been expended in the past decades to find and refine treatments for heart failure. These therapies include dietary and lifestyle modification, prescription medications, and even invasive interventions, which can range from implanted cardioverter-defibrillators and cardiac resynchronization therapy to mechanical circulatory support and transplantation.

However, despite the great advances in invasive interventions, pharmacological therapy remains the cornerstone of management. Today, many different drug classes are used to treat patients with heart failure, but few have shown a survival benefit. Three of these mortality-lowering drug classes will be considered in this paper: beta-blockers (BBs), angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers (ACEi/ARBs), and aldosterone antagonists (AAs).[3,4,5,6,7,8] It is important to note that these survival benefits have been shown only in patients with systolic dysfunction, i.e. heart failure with reduced ejection fraction (HFref).

This study uses the Medical Expenditure Panel Survey from years 2002 to 2016 to illuminate trends in the utilization of and associated expenditures on BBs, ACEi/ARBs, and AAs. Given the push for increased heart failure awareness and adherence to guideline-directed medical therapy over the past years, these results may shed some light on the success of these efforts to date. They may also provide independent verification of previous studies examining the use of mortality-lowering medications for heart failure.

(Note: This paper is heavily inspired by "National Trends in Statin Use and Expenditures in the US Adult Population From 2002 to 2013" by Salami et al, published in JAMA Cardiology in 2017.[9] The data source, methodological approach, and structure of the write-up closely follow Salami et al study; what has been changed is the medication of interest [from statins to BBs, ACEi/ARBs, and AAs] and population [from adults over 40 years of age to adults with a diagnosis of heart failure.]. The Salami et al study will therefore be referenced many times throughout the course of this paper.)

Methods

Study Design and Population

I performed a 15-year longitudinal, retrospective panel study of US adults with a diagnosis of heart failure using the 2002-2016 MEPS database. The MEPS is a source of "nationally representative data from 1996 to the present on health status, medical conditions, healthcare utilization, and healthcare expenditures for the U.S. civilian, non-institutionalized population."[10] The technical features and design of the survey have been described in minute detail on the AHRQ website;[11] please refer to the aforementioned paper by Salami et al for an excellent and succinct description of the survey. All data files used in this study were de-identified and available for public use, and thus not subject to institutional review board approval.

For each year included in the study, three different types of MEPS data files were required: full year consolidated, which contains information such as age, sex, income, etc; medical conditions, which catalogs each respondents' medical diagnoses; and prescribed medications. Although the medical conditions and prescribed medications files used were downloaded directly from the AHRQ website, the full year consolidated files were acquired using the services of IPUMS Health Surveys, which allowed for the creation of customized data extracts (samples and variables) and came with improved documentation.

The medical conditions files were filtered to only include individuals with a diagnosis of heart failure, as denoted by ICD9 and ICD10 codes of 428 and I50, respectively. (The MEPS transitioned to ICD10 in 2016.) The prescribed medications files were then filtered to only preserve the prescriptions of these selected individuals. All instances of beta-blocker, ACEi, ARB, and aldosterone antagonist use were noted. New variables were created to note the number of prescriptions, total expenditure, and out of pocket expenditure. Finally, these files were joined with the full-year consolidated files to form a data frame in which each row was a unique individual with heart failure, and each column was either a demographic or medication-related variable.

The data was pooled into 3-year cycles to increase per-period sample sizes and increase ease of analysis. Person-level weights were adjusted for pooling to ensure that later analysis was accurate. All respondents included in the study were age 18 and older and had a person-level weight greater than 0.

Medication Use and Expenditures

MEPS interviewees were prompted to report any and all medications prescribed and/or used by themselves or other members of their household. Information was recorded as given and permission was requested to contact the pharmacies of the respondents for further details regarding correct name, quantity, dosage, cost (both total and out-of-pocket by patient), and sources of payment. This was all done by the conductors of the MEPS. As mentioned previously, please refer to Salami et al for further details.

The drugs of interest in this study had the following Multum therapeutic codes: 47 (beta-blockers), 42 (angiotensin-converting enzyme inhibitors), 56 (angiotensin-receptor blockers), and 340 (aldosterone antagonists). These codes were used to filter the overall prescribed medicines MEPS files to only include instances in which one of these particular drugs were prescribed. For ease of analysis, angiotensin-converting-enzyme inhibitors and angiotensin-receptor blockers were later combined and considered to be the same drug class. Using this rich data, for each individual with heart failure, the following new variables were constructed for each medication of interest: a binary variable recording whether the individual had been prescribed the medication at all during the survey period, number of total prescriptions, total yearly cost, and total out-of-pocket cost.

Covariates

Age, sex, race/ethnicity, family income, type of insurance coverage, level of education, and regional location were included as covariates that could influence utilization of and expenditures on the medications of interest. The age of survey participants was cut into 3 groups: 64 year or younger, 65-74, 75 years or older. Race/ethnicity was grouped into 3 categories: white, black, or other. Family income, as a percentage of the federal poverty level (FPL), was grouped into 5 categories: poor (<100% of FPL), near poor (between 100 and 125% of FPL), low (between 125 and 200% of FPL), middle (between and 200 and 400% of FPL), high (> 400% of FPL). The study had 3 categories of insurance coverage: private only, any public, and uninsured. There were also 3 categories of educational attainment: less than high school or GED equivalent, high school or GED equivalent, and some college or greater. Regional location was cut into 4 categories: northeast, midwest, south, west. I regret the lack of further granularity within each of these covariates, especially with respect to race/ethnicity, but adequate sample sizes for analysis were prioritized.

Statistical Analysis

All data importation, tidying, transformation, visualization, and modelling was conducted with the open-source statistical software R, along with supporting add-on packages such as tidyverse, survey, foreign, tableone, broom, and stargazer.[12,13,14,15,16,17,18] The survey package assisted in accounting for the complex multi-stage sampling design of the MEPS; all analysis incorporated the relevant sample weights, primary sampling units, and strata for accurate point and standard error estimates. The svymean function was used to estimate the proportion of individuals using the medication of interest, average overall expenditures per person, and average out-of-pocket expenditures per person. The svyby function was used throughout the study to compare within groups (i.e. the percentage of individuals with heart failure taking beta-blockers stratified by region).

Predictors of use of the medications of interest were explored via multivariate logistic regression, with all aforementioned covariates included as potential predictors. Odds ratios were reported with 95% confidence intervals. In accordance with convention, p-values less than 0.05 were considered statistically significant.

Results

Overall Population Characteristics

Overall, there were 2994 MEPS respondents eligible for inclusion in this study from 2002-2016. The mean age was in the low 70s, with a majority or plurality greater than or equal to 75 years of age in all study periods. The subjects were mostly white, and there was a moderate female predominance in most years. Approximately half of the respondents belonged to the middle- or high-income categories and majority had attained at least a high school degree or GED equivalent. A plurality of respondents were from the south, while the west was the least represented region. A complete breakdown of the characteristics of this population -- i.e. adults with heart failure -- is given in **Table 1**.

Trends in BB, ACEi/ARB, and AA Use

The estimated usage of BBs in the study population over time is shown in **Figure 1**. The number of adults with heart failure reporting BB use increased from 46.3% in 2002-2004 to 68.8% in 2014-2016. This rise in utilization was statistically significant. Much of the gains were made in the period from 2002-2004 to 2008-2010, when it jumped to 66.1% and then stabilized in the mid-high 60s for the remainder of the study. The estimated usage of ACEi/ARBs in the study population is shown in **Figure 2**. The number of adults with heart failure reporting ACEi/ARB use did not change significantly over the study period, with utilization stable around approximately 60%. The estimated usage of AAs is shown in **Figure 3**. The number of adults with heart failure reporting AA use also did not change significantly over the study period. The percentage of individuals using AAs remained in the mid 10s.

Predictors of BB, ACEi/ARB, and AA Use

As per a multivariate logistic regression analysis, individuals aged 65-74 years were less likely to report BB use relative to individuals less than 65 years of age (OR, 0.815; 95% CI, 0.69-0.96). Women were also less likely to be using a BB, with an OR of 0.66 (95% CI, 0.53-0.83). Finally, middle income (200% - 399% of federal poverty limit) individuals had lower levels of BB use (OR, 0.75; 95% CI, 0.58-0.96). There were no statistically significant differences with respect to race, insurance coverage, educational attainment, or location. Individuals who were aged 65-74 years or 75 and older were less likely to be utilizing ACEi/ARBs, with ORs of 0.75 (95% CI, 0.62 - 0.91) and 0.79 (95% CI, 0.64 - 0.98), respectively.

Otherwise, there were no statistically significant within-group variations of ACEi/ARB use. Other than decreased reported use among the uninsured (OR, 0.39; 95% CI, 0.17 - 0.88), there were no statistically significant variations with respect to age, race, income, education, or location. Regression outputs are shown in **Table 2**.

Trends in BB, ACEi/ARB, and AA Expenditure

Mean overall expenditure on BBs per individual showed a decrease from $421 to $264 from the period between 2002-2004 and 2014-2016. The nadir of point estimates was $187 during 2011-2013. Examination of mean overall expenditures on ACEi/ARBs also revealed a decline from $383 to $174 over the study period. The majority of the decrease occurred between 2005-2007 and 2008-2010. Finally, despite volatile point estimates, mean overall expenditures on AAs also decreased from $129 to $73 over the study period. All of these changes were statistically significant. Trends for the mean overall costs, per user, of all three medication classes of interest are shown in **Figure 4**. Mean out-of-pocket costs for BBs fell from $207 to $31 over the length of the study, with the largest drop occurring between 2005-2007 and 2008-2010. Likewise, out-of-pocket costs for ACEi/ARBs and AAs declined from $222 to $29 and $88 to $20, respectively. All changes were statistically significant. Trends for the mean out-of-pocket costs, per user, of all three medication classes of interest are shown in **Figure 5**.

Discussion

In this study of a population of US adults with heart failure, we examined trends in the use and costs of three mortality-lowering drug classes between 2002 and 2016. The upshot is that BB usage increased over the study period, but ACEi/ARB and AA use remained constant. Importantly, uptake was far from optimal in all three medications classes. Although statistically significant predictors of use were found for each medication of interest, there were no predictors which affected all three medication classes. Costs, both total and out-of-pocket, decreased appreciably throughout the study period for all three medications of interest.

Although ACEi/ARB and AA use did not change over the study period, BB use increased by 49%, from 46.2% to 68.7% of respondents. Overall, at the end of the study in 2016, the rates of BB, ACEi/ARB, and AA use were 68.7%, 61.1% and 16.3%, respectively. With the exception of the AAs, these results are broadly consistent with other studies that have examined this issue in the recent past. For example, a study published in JACC in 2018 examining a robust outpatient registry of heart failure patients showed BB and ACEi/ARB utilization rates of 67.0% and 60.5%, respectively.[19] AA use, on the other hand, was 33.4% in that study; it is unclear why use is so much lower in this current study analyzing the MEPS. In any case, it is apparent that uptake of all three drug classes was less than optimal. Given the prevalence of heart failure, this suggests that there are meaningful improvements in morbidity and mortality at both the individual and population levels that have not yet been realized. The reasons for the suboptimal utilization are not entirely clear, but it has been postulated that both patient- and provider-related factors are involved. There have been several large-scale quality improvements studies that seek to increase the utilization of guideline-directed medical therapy, such as IMPROVE HF, and many have been effective, indicating that therapy can be optimized with concerted effort and surveillance.[20]

With healthcare spending approaching almost 18% of U.S. GDP, costs are often at the forefront of health policy discussions.[21] This study provides information that may be of use to stakeholders across the healthcare space, from clinicians to policy makers. Both total and out-of-pocket costs for BBs, ACEi/ARBs, and AAs showed statistically significant downward trends. Total costs decreased by 37%, 55%, and 44% for BB, ACEi/ARBs, and AAs, respectively; out-of-pocket costs decreased by 85%, 87%, and 78%, respectively. The out-of-pocket cost point estimates for BBs and ACEi/ARBs in the 2014-2016 period are consistent with contemporary studies, but AA cost estimates are unusually low, for reasons that are not particularly clear.[22] Despite these large percentage decreases in out-of-pocket costs across the board, only BBs showed an increase in utilization over the course of this study. This result is supported by recent research showing that patients are sensitive to the price of BBs but not ACEi/ARBs.[23] As mentioned in the introduction, heart failure is the leading cause of hospitalizations in the Medicare population; heart failure-related expenditures have been estimated to cross $30 billion. Increased financial assistance with payment for medications may not only decrease morbidity and mortality through increased adherence to guideline-directed medical therapy, but also result in substantial monetary savings for health systems and individuals via decreased rates of hospitalization and disease progression.

Limitations

This study, as constituted, has several limitations which the reader should keep in mind while examining this paper. (1) Although all individuals included in this study have a diagnosis of heart failure, it is not clear whether this is heart failure with reduced or preserved ejection fraction. The mortality lowering effects of BB, ACEi/ARBs, and AAs have been shown only for heart failure with reduced ejection fraction. (2) This study only considered whether the individual ever reported a prescription for a drug of interest over the course of a year. Medication doses are not accounted for at all. (3) There is no data regarding which heart failure class each individual is in. (4) There are some concerns about generalizability, given that the study population had moderately strong female predominance throughout. (Per other studies, the incidence of heart failure is approximately equal among the sexes.) (5) The study population consists only of non-institutionalized individuals, and thus does not reflect the experiences of those living in facilities such as nursing homes. (6) The dollar values for expenditures were not adjusted for inflation.

Conclusion

In conclusion, uptake of BBs, ACEi/ARBs, and AAs in individuals with heart failure has been and continues to be suboptimal. Only BBs showed a meaningful increase from 2002 to 2016. All mortality-lowering drug classes studied in this paper showed significant decreases in both total and out-of-pocket costs in the study period. Heart failure's combination of high prevalence and significant associated morbidity and mortality requires continued attention to pharmacological regimens from front-line clinicians, professional society leaders, and policy makers, among others.

Table 1

Characteristics	Adults, %					P value
	2002-2004	2005-2007	2008-2010	2011-2013	2014-2016	
No. of adults	2,040,852	2,0421,84	2,090,326	1,763,178	2,133,238	
Age, mean(SE), y	74.25 (14.58)	71.35 (14.96)	71.24 (16.43)	71.10 (15.21)	71.48 (14.14)	0.039
Age category, y						0.177
≤ 64	24.9	33.5	33	35.5	29.8	
65-74	23.4	21.2	22.3	18.6	27	
≥ 75	51.6	45.3	44.7	45.9	43.2	
Sex						0.1
Male	42.8	45.3	45.2	40.3	51.9	
Female	57.2	54.7	54.8	59.7	48.1	
Race/ethnicity						<0.001
White	83.9	85.5	81.7	79.6	77.2	
Black	14.1	12.6	14.4	17.8	15.6	
Other	2	1.9	3.9	2.6	7.2	
Family Income Level						0.085
Poor	13.7	13.5	17.9	20.8	18.1	
Near poor	6.4	8.9	8.9	8.1	4.9	
Low	25	23.4	21.6	18.6	20.4	
Middle	34.5	27.1	26.9	30.4	30.5	
High	20.5	27.1	24.7	22.1	26	
Insurance Status						0.026
Private	50.5	53.5	41.6	45.7	50.8	
Any Public	46.8	42.1	53.2	52.2	47	
Uninsured	2.7	4.4	5.1	2.1	2.2	
Educational Attainment						<0.001
< High School	36.5	27	27.6	63.9	69.4	
High School/GED Equivalent	47	50.3	51.9	27.9	19.6	
≥ Some college	16.5	22.7	20.5	8.2	11	
Region						0.543
Northeast	27.1	27.6	21.5	21.1	21.2	
Midwest	22.6	24.1	26.8	25.6	26	
South	35.4	37.8	34.2	39.3	38.7	
West	14.9	10.5	17.4	13.9	14.2	

Figure 1

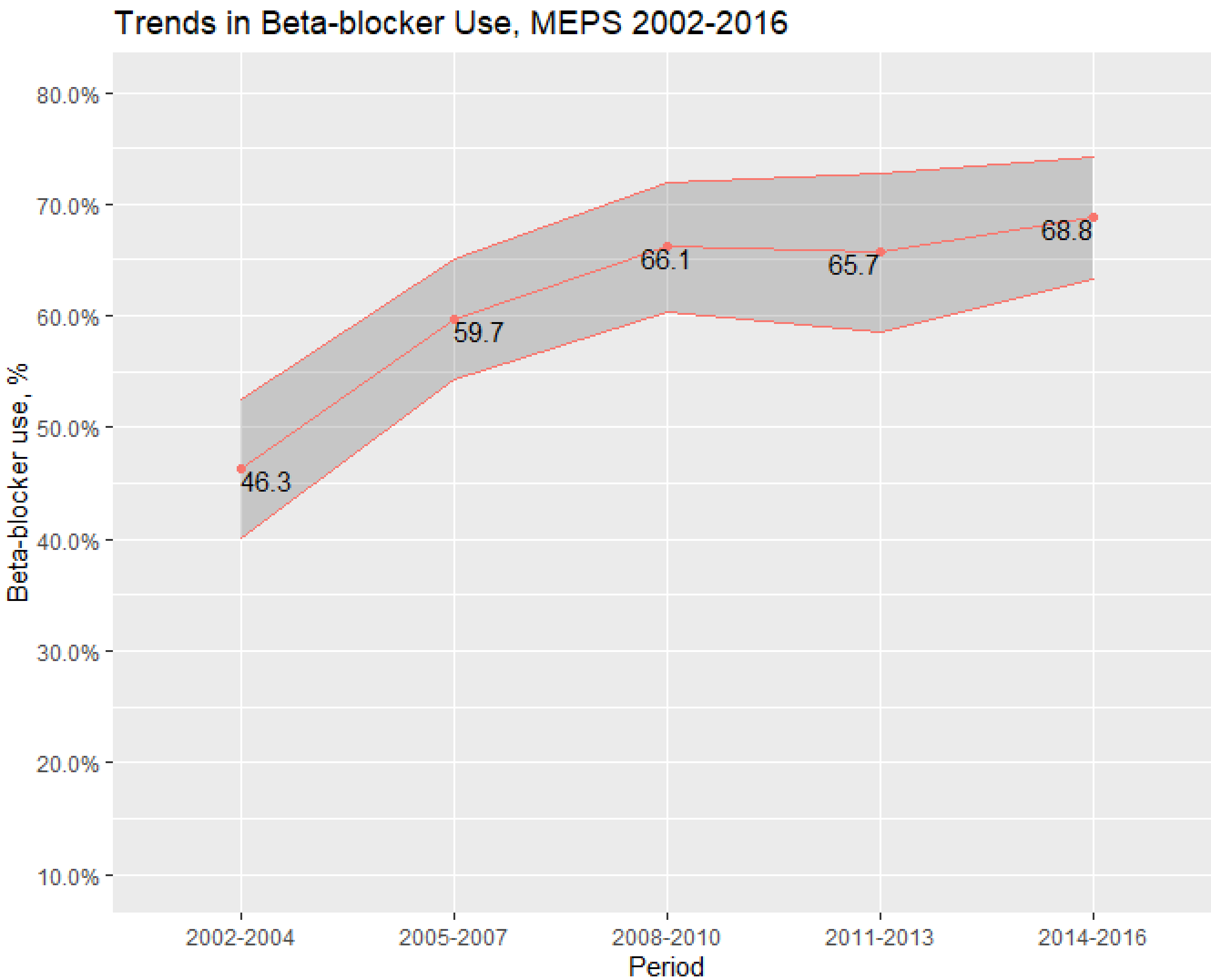
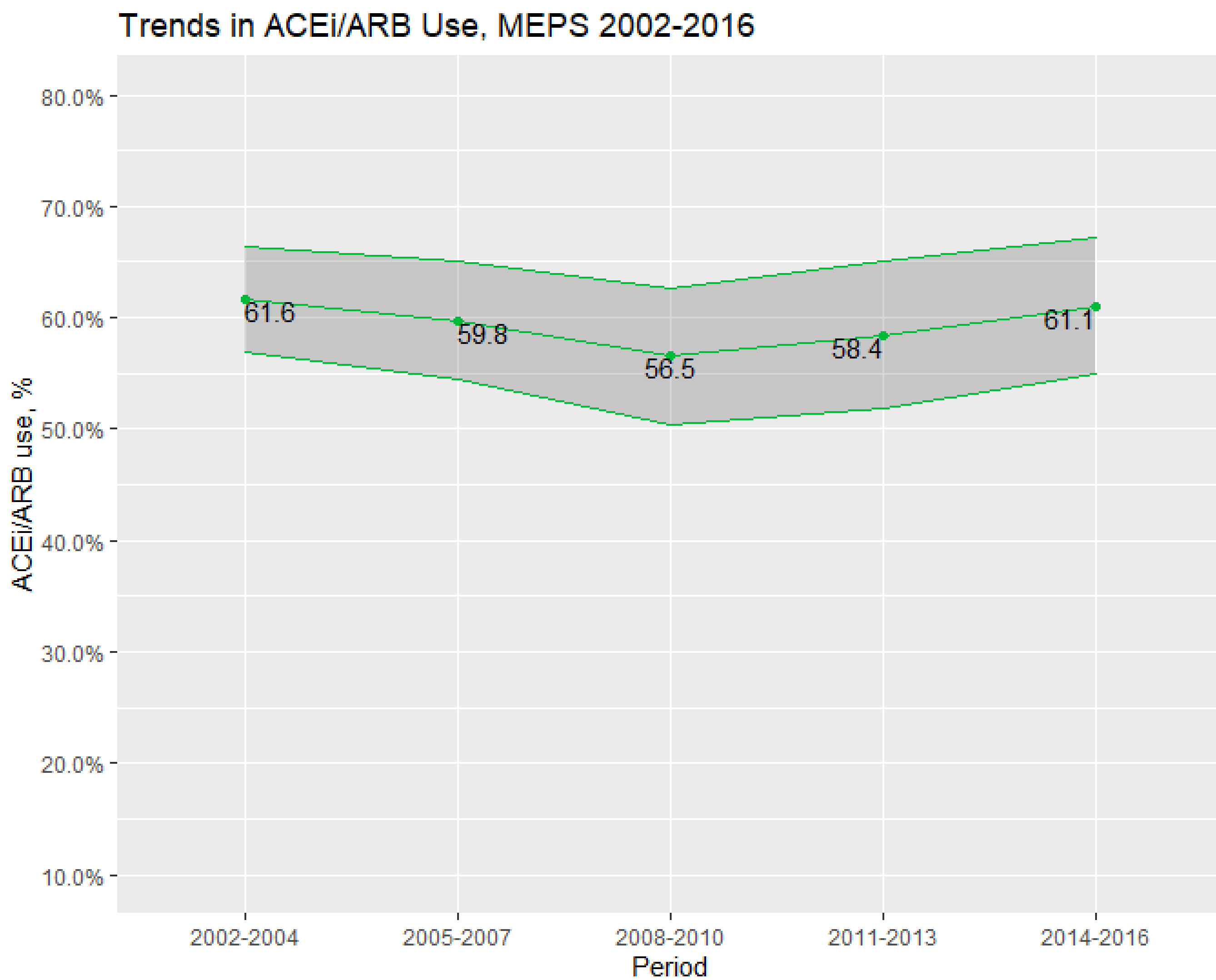
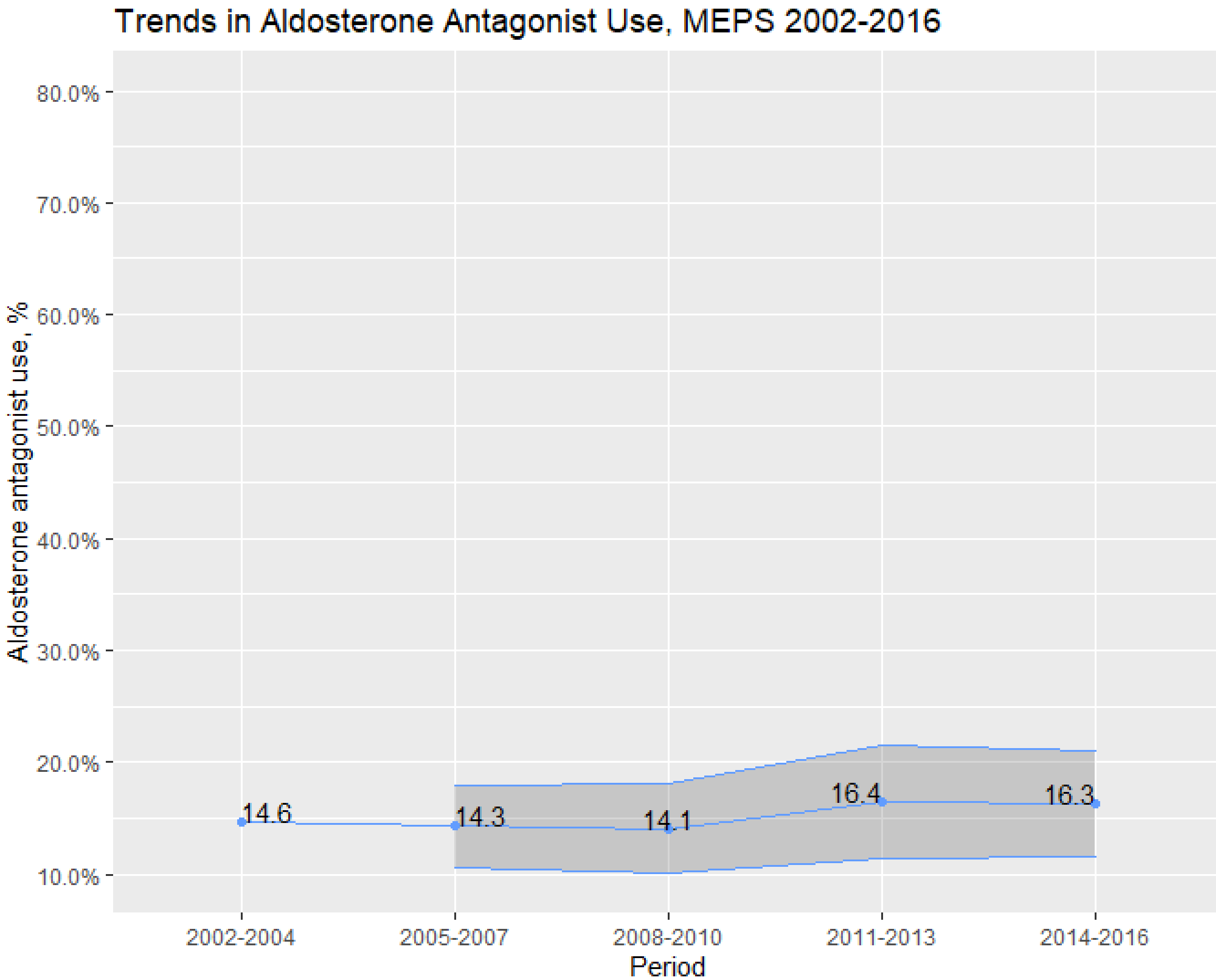

Trends in Beta-blocker Use, MEPS 2002-2016
Beta-blocker use, %
80.0%
70.0%
60.0%
50.0%
40.0%
30.0%
20.0%
10.0%
46.3
59.7
66.1
65.7
68.8
2002-2004
2005-2007
2008-2010
2011-2013
2014-2016
Period

Figure 2



Trends in ACEi/ARB Use, MEPS 2002-2016
80.0%
70.0%
60.0%
50.0%
40.0%
30.0%
20.0%
10.0%
ACEi/ARB use, %
61.6
59.8
56.5
58.4
61.1
2002-2004
2005-2007
2008-2010
2011-2013
2014-2016
Period

Figure 3

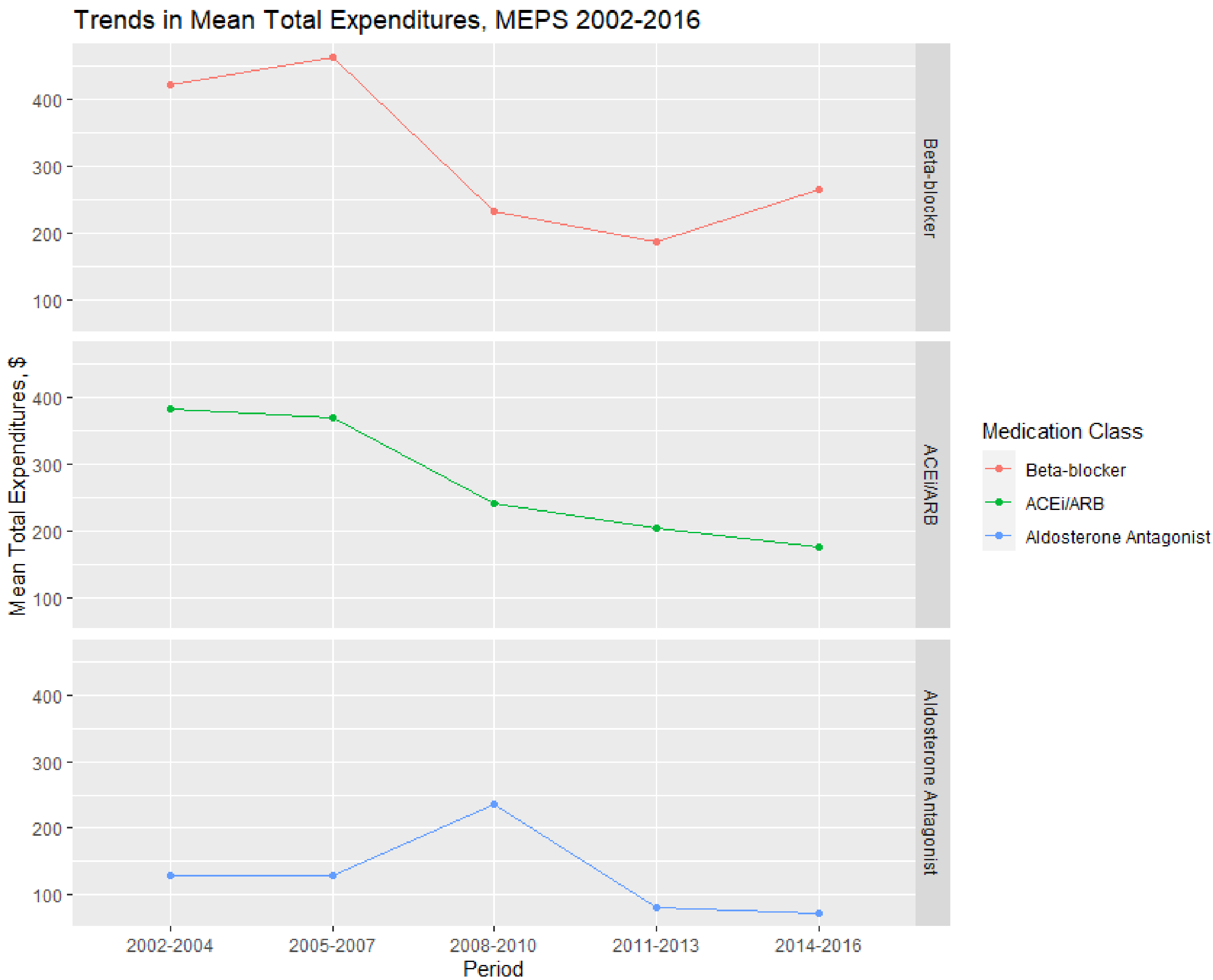


Trends in Aldosterone Antagonist Use, MEPS 2002-2016
80.0%
70.0%
60.0%
50.0%
40.0%
30.0%
20.0%
10.0%
Aldosterone antagonist use, %
14.6
14.3
14.1
16.4
16.3
2002-2004
2005-2007
2008-2010
2011-2013
2014-2016
Period

Table 2

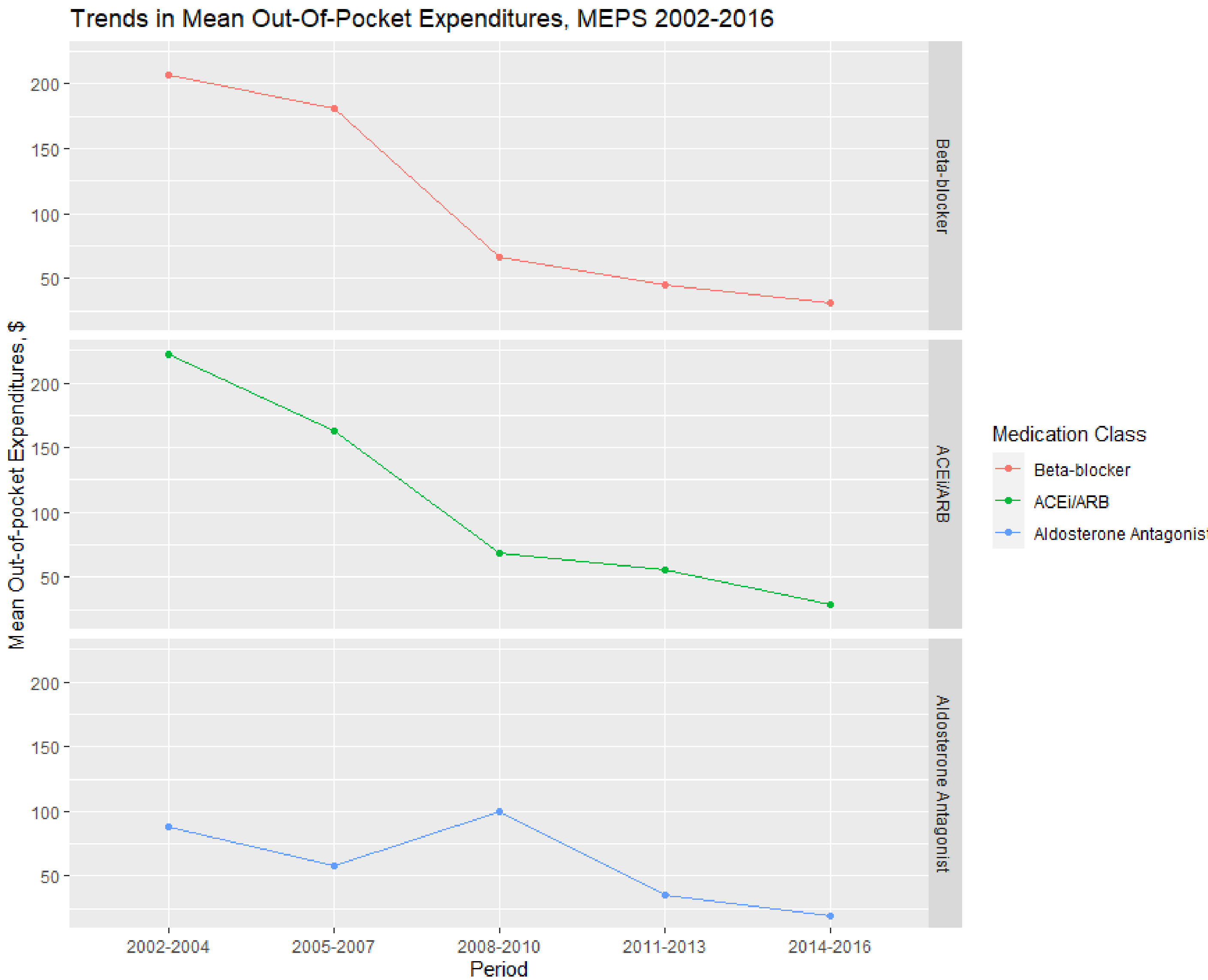
Variable	Odds Ratio (95% CI) BB	ACEi/ARB	AA
Age category, y			
≤ 64	1 [Reference]	1 [Reference]	1 [Reference]
65-74	0.815** (0.692, 0.961)	0.749*** (0.619, 0.906)	0.821 (0.632, 1.066)
≥ 75	0.893 (0.705, 1.130)	0.788** (0.636, 0.976)	0.835 (0.614, 1.136)
Sex			
Male	1 [Reference]	1 [Reference]	1 [Reference]
Female	0.661*** (0.525, 0.831)	0.809* (0.648, 1.009)	0.862 (0.630, 1.179)
Race/ethnicity			
White	1 [Reference]	1 [Reference]	1 [Reference]
Black	0.884 (0.689, 1.135)	0.834 (0.633, 1.099)	1.367* (0.951, 1.964)
Other	1.528 (0.851, 2.745)	1.059 (0.586, 1.911)	0.869 (0.410, 1.845)
Family Income Level			
Poor	1 [Reference]	1 [Reference]	1 [Reference]
Near poor	1.261 (0.952, 1.671)	0.977 (0.747, 1.278)	1.215 (0.822, 1.794)
Low	0.935 (0.729, 1.199)	1.014 (0.806, 1.275)	1.114 (0.845, 1.468)
Middle	0.746** (0.582, 0.955)	0.848 (0.676, 1.064)	1.157 (0.816, 1.641)
High	0.991 (0.783, 1.254)	0.923 (0.729, 1.169)	0.929 (0.674, 1.281)
Insurance Status			
Private	1 [Reference]	1 [Reference]	1 [Reference]
Any Public	1.060 (0.843, 1.334)	0.916 (0.715, 1.175)	0.787 (0.565, 1.095)
Uninsured	0.785 (0.488, 1.263)	0.869 (0.531, 1.422)	0.388** (0.171, 0.882)
Educational Attainment			
< High School	1 [Reference]	1 [Reference]	1 [Reference]
High School/GED Equivalent	1.148 (0.874, 1.509)	1.042 (0.806, 1.346)	1.229 (0.896, 1.687)
≥ Some college	1.058 (0.869, 1.289)	1.080 (0.883, 1.321)	0.924 (0.687, 1.244)
Region			
Northeast	1 [Reference]	1 [Reference]	1 [Reference]
Midwest	1.445* (0.993, 2.103)	1.337* (0.973, 1.838)	1.273 (0.741, 2.188)
South	1.289 (0.922, 1.802)	1.124 (0.828, 1.525)	1.056 (0.634, 1.760)
West	0.972 (0.675, 1.400)	1.384* (0.956, 2.002)	0.991 (0.544, 1.807)
Constant	1.665*** (1.177, 2.354)	1.618*** (1.199, 2.183)	0.203*** (0.127, 0.326)
Observations	2,994	2,994	2,994
Note:			*p<0.1; **p<0.05; ***p<0.01

Figure 4



Trends in Mean Total Expenditures, MEPS 2002-2016
Mean Total Expenditures, $
400
300
200
100
Beta-blocker
ACEi/ARB
Aldosterone Antagonist
2002-2004
2005-2007
2008-2010
2011-2013
2014-2016
Period
Medication Class
Beta-blocker
ACEi/ARB
Aldosterone Antagonist

Figure 5



Trends in Mean Out-Of-Pocket Expenditures, MEPS 2002-2016
Mean Out-of-pocket Expenditures, $
200
150
100
50
Beta-blocker
ACEi/ARB
Aldosterone Antagonist
2002-2004
2005-2007
2008-2010
2011-2013
2014-2016
Period
Medication Class
Beta-blocker
ACEi/ARB
Aldosterone Antagonist

References

1. Pfuntner A, Wier LM, Stocks C. Most frequent conditions in U.S. hospitals, 2011. Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project statistical brief #162. September 2013. https://www.hcup-us.ahrq.gov/reports/statbriefs/sb162.pdf.
2. Shah, Kevin S., et al. "Heart Failure With Preserved, Borderline, and Reduced Ejection Fraction." *Journal of the American College of Cardiology*, vol. 70, no. 20, 2017, pp. 2476–2486., doi:10.1016/j.jacc.2017.08.074.
3. "Effect of Metoprolol CR/XL in Chronic Heart Failure: Metoprolol CR/XL Randomised Intervention Trial in-Congestive Heart Failure (MERIT-HF)." *The Lancet*, vol. 353, no. 9169, 1999, pp. 2001–2007., doi:10.1016/s0140-6736(99)04440-2.
4. Packer, Milton, et al. "Effect of Carvedilol on the Morbidity of Patients With Severe Chronic Heart Failure." *Circulation*, vol. 106, no. 17, 2002, pp. 2194–2199., doi:10.1161/01.cir.0000035653.72855.bf.
5. "Effects of Enalapril on Mortality in Severe Congestive Heart Failure." *New England Journal of Medicine*, vol. 316, no. 23, 1987, pp. 1429–1435., doi:10.1056/nejm198706043162301.
6. Granger, Christopher B, et al. "Effects of Candesartan in Patients with Chronic Heart Failure and Reduced Left-Ventricular Systolic Function Intolerant to Angiotensin-Converting-Enzyme Inhibitors: the CHARM-Alternative Trial." *The Lancet*, vol. 362, no. 9386, 2003, pp. 772–776., doi:10.1016/s0140-6736(03)14284-5.
7. Pitt, Bertram, et al. "The Effect of Spironolactone on Morbidity and Mortality in Patients with Severe Heart Failure." *New England Journal of Medicine*, vol. 341, no. 10, 1999, pp. 709–717., doi:10.1056/nejm199909023411001.
8. Zannad, Faiez, et al. "Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms." *New England Journal of Medicine*, vol. 364, no. 1, 2011, pp. 11–21., doi:10.1056/nejmoa1009492.
9. Salami JA, Warraich H, Valero-Elizondo J, et al. National Trends in Statin Use and Expenditures in the US Adult Population From 2002 to 2013: Insights From the Medical Expenditure Panel Survey. JAMA Cardiol. 2017;2(1):56–65. doi:10.1001/jamacardio.2016.4700
10. Lynn A. Blewett, Julia A. Rivera Drew, Risa Griffin and Kari C.W. Williams. IPUMS Health Surveys: Medical Expenditure Panel Survey, Version 1.1 [dataset]. Minneapolis, MN: IPUMS, 2019. https://doi.org/10.18128/D071.V1.1
11. Medical Expenditure Panel Survey (MEPS). Content last reviewed August 2018. Agency for Healthcare Research and Quality, Rockville, MD.https://www.ahrq.gov/data/meps.html
12. R Core Team (2019). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.
13. Wickham et al., (2019). Welcome to the tidyverse. Journal of Open Source Software, 4(43), 1686, https://doi.org/10.21105/joss.01686
14. T. Lumley (2004) Analysis of complex survey samples. Journal of Statistical Software 9(1): 1-19
15. R Core Team (2019). foreign: Read Data Stored by 'Minitab', 'S', 'SAS', 'SPSS', 'Stata', 'Systat', 'Weka', 'dBase', ... R package version 0.8-72. https://CRAN.R-project.org/package=foreign
16. Kazuki Yoshida (2020). tableone: Create 'Table 1' to Describe Baseline Characteristics. R package version 0.11.1. https://CRAN.R-project.org/package=tableone
17. David Robinson and Alex Hayes (2020). broom: Convert Statistical Analysis Objects into Tidy Tibbles. R package version 0.5.5. https://CRAN.R-project.org/package=broom
18. Hlavac, Marek (2018). stargazer: Well-Formatted Regression and Summary Statistics Tables. R package version 5.2.1. https://CRAN.R-project.org/package=stargazer
19. Greene SJ, Butler J, Albert NM, DeVore AD, Sharma PP, Duffy CI, Hill CL, McCague K, Mi X, Patterson JH, Spertus JA, Thomas L, Williams FB, Hernandez AF, Fonarow GC. Medical therapy for heart failure with reduced ejection fraction: the CHAMP-HF Registry. J Am Coll Cardiol. 2018;72:351–366. doi: 10.1016/j.jacc.2018.04.070.
20. Fonarow G.C., Albert N.M., Curtis A.B., et al. (2010) Improving evidence-based care for heart failure in outpatient cardiology practices: primary results of the registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE HF). Circulation 122:585–596.
21. Hartman, Micah, et al. "National Health Care Spending In 2018: Growth Driven By Accelerations In Medicare And Private Insurance Spending." *Health Affairs*, vol. 39, no. 1, 2020, pp. 8–17., doi:10.1377/hlthaff.2019.01451.
22. Mcgee, Blake Tyler, et al. "Prescription Drug Spending and Medication Adherence Among Medicare Beneficiaries with Heart Failure." *Journal of Managed Care & Specialty Pharmacy*, vol. 25, no. 6, 2019, pp. 705–713., doi:10.18553/jmcp.2019.25.6.705.
23. Ibid.