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Off-label Utilization of Antihypertensive Medications in Children

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Abstract

Objective— To examine off-label utilization and costs of antihypertensive drugs in children using a national sample of prescription claims.

Design— Cross-sectional study.

Setting— 2002 Medstat MarketScan Database, a national sample of outpatient prescription claims of children ≤ 18 years old enrolled in private, employer-sponsored health plans.

Main Outcome Measures— Off-label use of antihypertensive drugs by patient age and costs of antihypertensives calculated as mean cost per child per 30-day fill.

Results— One-half of the index antihypertensive prescription claims were off-label, based on minimum age criteria. Boys were more likely (56%) than girls (46%) to be prescribed off-label antihypertensives ($p < 0.001$). Children aged ≥ 12 years were more likely to be prescribed off-label antihypertensives (53%) compared with children aged ≤ 5 (46%) and 6–11 years (42%, $p < 0.001$). Off-label use varied significantly by class of antihypertensive drugs ($p < 0.001$). Overall, off-label antihypertensives were significantly more expensive than on-label antihypertensives.

Conclusions— Despite availability of often less expensive on-label alternatives for the same class of antihypertensive drugs, off-label antihypertensive drugs were prescribed frequently in children. These findings underscore the potential clinical and economic implications of common off-label prescribing, for children, their parents, physicians and payers.

Keywords

off-label; FDA; hypertension; antihypertensive drugs; children

INTRODUCTION

Off-label use of medications – the use of medications for an age or indication outside of the drug label – is a common practice in pediatrics, because many medications are not labeled for

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use in children.^{1–9} Most studies of off-label drug use in children have been conducted in countries outside of the United States, which have different drug licensing and regulatory systems and therefore limited applicability to U.S. practice.^{6,9–14} However, a U.S. study published in 2007 found that 79% of hospitalized children received an off-label drug; older children were more likely to receive an off-label drug, boys were more likely than girls to receive an off-label cardiac drug, and off-label use varied by drug class.¹⁵ In one year, off-label use accounted for over \$270 million, or 40% of the total dollars, spent on these drugs.¹⁵

We propose to study off-label use of medications in U.S. children in the outpatient setting as a complement to this recently published inpatient study. From our study of medications listed in the formulary of the *Harriet Lane Handbook* – a widely used pediatric reference source – we know that cardiac drugs (principally antihypertensive drugs) as a class had the highest proportion (57%) of medications without Food and Drug Administration (FDA) approved pediatric labeling.¹⁶

Therefore, we focused on antihypertensive medications for the present study and sought to quantify off-label use of these medications in children using a national sample of prescription claims. We sought to describe factors associated with off-label use of antihypertensive drugs in the outpatient setting including patient age, gender, drug cost, and class of antihypertensive drugs. Based on the published literature,^{15,17–19} we hypothesized that older children and boys would be more likely to receive off-label antihypertensive drugs than younger children and girls respectively. We also hypothesized that there may be an economic incentive to prescribe off-label drugs due to lower costs of older, off-patent antihypertensive medications that have generic equivalents but not pediatric labeling. Accordingly, patterns of outpatient off-label prescribing including variations in patient characteristics and medication costs may be important to families and insurance plans that may be clinically and/or economically affected by such prescribing patterns.

METHODS

Study Design

We conducted secondary analyses of cross-sectional data to examine off-label utilization and costs of five classes of commonly used long-term antihypertensive medications (angiotensin converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], β -blockers, calcium [Ca²⁺] channel blockers, diuretics) in children ≤ 18 years old during a 12-month period from January 1, 2002, to December 31, 2002. The study was approved by the Institutional Review Board of the University of Michigan Medical School.

Data Source

We used the Medstat 2002 MarketScan Commercial Claims and Encounter Database (Thomson Medstat Inc., Ann Arbor, MI), a nationwide database of person-level health care utilization and expenditure data for enrollees in approximately 100 employer-sponsored benefit plans offered by more than 40 large employers across the country. This database contains prescription drug claims, which we used to evaluate our study's primary objective. The database also includes beneficiary enrollment information, although information on children's race/ethnicity or measures of socioeconomic status are not reported.

Study Sample

The study sample consisted of outpatient prescription claims for the five classes of commonly used long-term antihypertensive medications among children ≤ 18 years old who were continuously enrolled for >320 days during the calendar year. We identified antihypertensive drugs individually using the variable THRD TDS (Therapeutic Detail Code Description) and

as a class using the variable THERCLS (Therapeutic Class) from the Red Book™ files included in the Medstat Database. Our evaluation focused on the five classes of antihypertensive drugs (ACE inhibitors, ARBs, β -blockers, Ca^{2+} channel blockers, diuretics) recommended as acceptable classes of antihypertensive drugs for treatment of blood pressure in children by the widely used consensus recommendations, the Fourth Report on the Diagnosis Evaluation and Treatment of High Blood Pressure in Children, published by the National High Blood Pressure Education Program.²⁰ It was possible that a single patient could have multiple prescription claims during the 12-month time frame. To mitigate the effects of possible non-independence of prescription claims, we chose to examine only the first prescription claim in the database for each patient during the study year which we refer to heretofore as the index prescription claim.

Antihypertensive Medication Use

Our study had two outcomes of interest: off-label use of antihypertensive medications and the cost of antihypertensive medications. We classified off-label use of antihypertensive drugs by patient age criteria regardless of indication for use.¹⁵ We considered prescriptions for antihypertensive drugs without pediatric labeling as off-label. Prescriptions for antihypertensive drugs to children not meeting minimum age criteria on the pediatric label of a given medication were also considered off-label; those for children meeting minimum age criteria were considered on-label, regardless of indication. We considered all prescriptions for antihypertensive medications with pediatric labeling, but without specific age criteria, on-label. Thus if an antihypertensive medication was prescribed for the approved age group, but for a condition not approved on the pediatric label, the prescription claim was still considered on-label. We used this approach to classify off-label use because diagnoses are not reported for each prescription claim.

We identified pediatric labeling information of each antihypertensive medication using the drug summaries found in the Thomson Micromedex Healthcare Series, accessed online.²¹ To be contemporaneous with our data source from 2002, we cross-referenced pediatric labeling information with the FDA website providing pediatric labeling changes since 1997.²²

Cost of Antihypertensive Medications

To standardize the cost measure among children with various duration of medication use, we assessed cost of antihypertensive drugs as the mean cost per child for a 30-day supply of the prescribed drug. The cost per child for a 30-day supply was calculated as amount paid for prescription claim divided by (number of days of medication supply/30). Costs were assessed among children who had no evidence of other insurance coverage in addition to the plan represented in the Medstat Database. Children with evidence of claims having coordination of benefits payments (i.e., with coverage from more than one payer) were assumed to have other sources of insurance coverage and were excluded from the final dataset and cost analyses.

Analyses

We obtained descriptive statistics of the cost measure overall and for each combination of class of antihypertensives and off-label status. We performed a two-sample *t*-test with equal variance to compare off-label use and cost per child for a 30-day supply.

We used the Pearson chi-square to test bivariate comparisons between off-label use and independent variables (age group, gender, class of antihypertensive medications). Patient age at the time each prescription was filled was determined and classified into 3 age groups: ≤ 5 years, 6–11 years, and ≥ 12 years, according to commonly identified minimum age criteria for FDA-approved pediatric use. We conducted stratified chi-square analyses between off-label use and class of antihypertensive medications by patient gender and age group.

To evaluate the magnitude of the associations between off-label use and class of antihypertensive medications, we calculated adjusted odds ratios using multivariate logistic regression controlling for patient age and gender. We chose diuretics as the reference group for all analyses because, among the five classes of antihypertensive drugs evaluated, diuretics had the highest proportion of medications with pediatric labeling. Similarly, we chose the oldest age group (≥ 12 years) as the reference group since this age group was most likely to have pediatric indications for use of antihypertensive drugs. We hypothesized that patient age might have distinct effects on off-label use across different classes of antihypertensive medications. For example, all of the ARBs used in children in the youngest age group (≤ 5 years) would be off-label since all 6 ARBs evaluated in the study were off-label for these ages. Therefore, we further analyzed the drug class – off-label relation stratified by age group and controlling for gender. All results of the multivariate model are therefore shown according to age group. We considered p -values less than 0.05 to indicate statistical significance. All statistical analyses were conducted using STATA 8.2 (Stata Corp., College Station, TX).

RESULTS

Sample Characteristics

Of the 944,502 children in the 2002 database, 4,317 children (0.5%) had at least one prescription claim for an antihypertensive drug. Among these children, there was a total of 19,109 prescription claims for 47 different antihypertensive medications representing the five classes of antihypertensive drugs studied. Two-thirds of children had more than one antihypertensive prescription claim during the study year. The final dataset included the index prescription claim for 3,660 unique children (85% of the initial sample) for whom 1) we had complete information on patient age, gender, drug class and drug cost and 2) there was no evidence of coordination of benefits with additional insurance plans outside of those represented in the database.

Among the 3,660 children who filled prescriptions for antihypertensive medications, slightly less than half were boys (45%) and there was a preponderance (73%) of older children (≥ 12 years). About 1 of every 7 children was prescribed 2 or more different antihypertensive drugs.

Off-Label Use of Antihypertensives for Children

One-half of the index antihypertensive prescription claims in 2002 were off-label. β -blockers comprised the class of antihypertensive drugs most frequently prescribed, followed by ACE inhibitors, diuretics, Ca^{2+} channel blockers, and ARBs respectively (Table 1). Off-label use varied by class of antihypertensive medications, with all Ca^{2+} channel blockers being prescribed off-label compared to smaller proportions of ARBs, ACE inhibitors, β -blockers, and diuretics ($p < 0.001$) (Table 1).

In bivariate analyses, children in the oldest age group (≥ 12 years) were more likely to be prescribed off-label antihypertensives (53%) compared to children in the youngest (≤ 5 years) and middle age groups (6–11 years) (46%, 42% respectively) ($p < 0.001$). Boys were more likely than girls to be prescribed off-label antihypertensives (56% vs. 46%) ($p < 0.001$).

In stratified bivariate analyses, we found substantive variation in the off-label proportion by class of antihypertensives, patient age group and gender, where the greatest variation by age group and gender of all antihypertensives was seen in diuretics ($p < 0.001$) (Table 2). All Ca^{2+} channel blockers were off-label for all age groups and ARBs were off-label for the youngest age group. Importantly, there were no on-label alternatives within these classes of antihypertensives for these age groups.

Gender-adjusted odds ratios stratified by age are presented in Table 3. All Ca²⁺ channel blockers for all age groups were off-label, thus the odds ratios were indeterminate. Boys were more likely to be prescribed off-label antihypertensive drugs compared to girls, controlling for patient age and class of antihypertensives. For children in the oldest age group, ACE inhibitors, ARBs, and β -blockers were more likely to be prescribed off-label than diuretics. Conversely, for children in the middle age group, ACE inhibitors, ARBs, and β -blockers were less likely to be prescribed off-label. For children in the youngest age group, ACE inhibitors and β -blockers were more likely to be prescribed off-label. In contrast, diuretics were significantly less likely to be prescribed off-label in the youngest age group compared with the older age groups.

Cost of Antihypertensives for Children

The mean cost of an antihypertensive drug per child per 30-day fill in 2002 was \$22.12 (95% CI: \$21.37–\$22.87). Overall, off-label antihypertensive drugs were statistically significantly more expensive compared to on-label antihypertensives, with the mean cost of an off-label antihypertensive per child per 30-day fill at \$23.48 (95% CI: \$22.26–\$24.69) compared to \$20.74 (95% CI: \$19.86–\$21.62) for an on-label antihypertensive ($p < 0.001$). However, we also found that the mean cost of an off-label and on-label antihypertensive drug per child per 30-day fill varied by class of antihypertensives: off-label β -blockers and diuretics were significantly less expensive than same-class on-label counterparts (Table 4).

DISCUSSION

We found that one-half of children ≤ 18 years of age for whom antihypertensive medications were prescribed in 2002 received an off-label drug in the outpatient setting. We found that off-label use of antihypertensives was positively associated with older age and male gender, consistent with findings from a recent U.S. study of medication use among hospitalized children.¹⁵ We also found that off-label antihypertensives were overall more expensive than their on-label counterparts. To our knowledge, this is the first study of off-label use and costs of antihypertensive medications in U.S. children in the outpatient setting. Our novel findings raise questions about factors that influence physicians' prescribing behavior, including patient characteristics and the labeling status of medications.

Until recently, previous studies of off-label drug use in U.S. children were limited to simple counts of medications listed in drug references, rather than prescriptions written for such medications.^{3,7,16} Studies using the Physician's Desk Reference (PDR) estimated that approximately 75% of medications were off-label for use in children because they had insufficient labeling information for pediatric use.^{3,7} We found in our study of pediatric labeling status of medications listed in the formulary of the *Harriet Lane Handbook* that 57% of cardiovascular medications did not have FDA-approved pediatric labeling.¹⁶

Importantly, our study indicates that even when on-label alternatives exist within the same class of antihypertensive medications, off-label antihypertensives are still prescribed. It is unknown whether off-label antihypertensives are prescribed because physicians are unaware of on-label alternatives, and/or whether off-label antihypertensives are prescribed because other potential factors such as insurance plan formularies are more influential than pediatric labeling status in the physician choice of antihypertensive medications.

We found that children in the oldest age group were consistently more likely to be prescribed off-label antihypertensive drugs compared to children in the youngest and middle age groups. We speculate that adolescents may be more likely to receive off-label antihypertensive drugs because physicians may extrapolate adult doses more frequently for this age group than for younger children.

Despite boys and girls being equally represented among antihypertensive users in our dataset, we found that boys were consistently more likely to be prescribed off-label antihypertensives compared to girls. Our finding is consistent with previous studies that have shown boys are more likely than girls to receive off-label medications, such as growth hormone for short stature.^{17–19}

We found that index off-label antihypertensives overall were more expensive from the payer perspective, compared with their on-label counterparts in 2002. However, older drugs with expired patent protection and generic equivalents, such as diuretics and β -blockers, were found to be less expensive prescribed off-label compared to their on-label counterparts in the same classes. To our knowledge, this is a novel finding not previously identified in studies of off-label drug use in children. This finding suggests there is a possible economic incentive for off-label antihypertensive use for diuretics and β -blockers from the payer perspective – which adds complexity for health plans that generally prioritize medications with generic equivalents but may also wish to promote use of medications with pediatric labeling in their formularies.

Limitations

Our study examined filled prescription claims of antihypertensive medications. Actual patient use of these medications may differ from patterns of use found in our study. Also, our study used 2002 claims data which may not reflect current utilization patterns of antihypertensives in children, because pediatric labeling changes have occurred during the interim time period. Our conservative definition of off-label use in our analysis that did not include off-label use by indication may have resulted in underestimation of off-label use of antihypertensive medications in children. Our consideration of prescription claims for antihypertensive medications approved for pediatric use without specific age criteria to be on-label for all ages may have also resulted in underestimation of off-label use of antihypertensive medications.

In addition, our findings pertain to children enrolled in employer-sponsored benefit plans and may not be generalizable to other children without prescription medication coverage or children with public coverage such as Medicaid. Furthermore, we did not evaluate factors that predicted which children would receive antihypertensive medications, particularly off-label antihypertensives; further assessment of demographic characteristics (including race/ethnicity and measures of socioeconomic status) is important. In addition, patterns of off-label use of antihypertensive medications in children may be further illuminated by future investigations of provider prescribing practices of these drugs. Finally, there were no clinical outcomes of antihypertensive medication use available for study from this dataset.

CONCLUSIONS

Despite the availability of multiple on-label alternatives, one-half of outpatient prescription claims for antihypertensive medications in this national sample of children were off-label in 2002. Findings from our outpatient study and the recent inpatient study of off-label use among hospitalized children highlight the need to understand the clinical and economic implications of frequent off-label physician prescribing practices.

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References

1. Guidelines for the ethical conduct of studies to evaluate drugs in pediatric populations. Committee on Drugs, American Academy of Pediatrics. *Pediatrics* Feb;1995 95(2):286–294. [PubMed: 7838651]
2. Unapproved uses of approved drugs: the physician, the package insert, and the Food and Drug Administration: subject review. American Academy of Pediatrics Committee on Drugs. *Pediatrics* Jul; 1996 98(1):143–145. [PubMed: 8668390]
3. Blumer JL. Off-label uses of drugs in children. *Pediatrics* Sep;1999 104(3 Pt 2):598–602. [PubMed: 10469797]
4. Steinbrook R. Testing medications in children. *N Engl J Med* Oct 31;2002 347(18):1462–1470. [PubMed: 12409558]
5. Wilson JT. An update on the therapeutic orphan. *Pediatrics* Sep;1999 104(3 Pt 2):585–590. [PubMed: 10469794]
6. Conroy S, Choonara I, Impicciatore P, et al. Survey of unlicensed and off label drug use in paediatric wards in European countries. European Network for Drug Investigation in Children. *BMJ* Jan 8;2000 320(7227):79–82. [PubMed: 10625257]
7. Cote CJ, Kauffman RE, Troendle GJ, Lambert GH. Is the “therapeutic orphan” about to be adopted? *Pediatrics* Jul;1996 98(1):118–123. [PubMed: 8668382]
8. McIntyre J, Conroy S, Avery A, Corns H, Choonara I. Unlicensed and off label prescribing of drugs in general practice. *Arch Dis Child* Dec;2000 83(6):498–501. [PubMed: 11087285]
9. t Jong GW, Vulto AG, de Hoog M, Schimmel KJ, Tibboel D, van den Anker JN. Unapproved and off-label use of drugs in a children’s hospital. *N Engl J Med* Oct 12;2000 343(15):1125. [PubMed: 11032528]
10. t Jong GW, van der Linden PD, Bakker EM, et al. Unlicensed and off-label drug use in a paediatric ward of a general hospital in the Netherlands. *Eur J Clin Pharmacol* Jul;2002 58(4):293–297. [PubMed: 12136376]
11. t Jong GW, Vulto AG, de Hoog M, Schimmel KJ, Tibboel D, van den Anker JN. A survey of the use of off-label and unlicensed drugs in a Dutch children’s hospital. *Pediatrics* Nov;2001 108(5):1089–1093. [PubMed: 11694685]
12. Turner S, Longworth A, Nunn AJ, Choonara I. Unlicensed and off label drug use in paediatric wards: prospective study. *BMJ* Jan 31;1998 316(7128):343–345. [PubMed: 9487167]
13. Bajcetic M, Jelisavcic M, Mitrovic J, et al. Off label and unlicensed drugs use in paediatric cardiology. *Eur J Clin Pharmacol* Nov;2005 61(10):775–779. [PubMed: 16151762]
14. Pandolfini C, Impicciatore P, Provasi D, Rocchi F, Campi R, Bonati M. Off-label use of drugs in Italy: a prospective, observational and multicentre study. *Acta Paediatr* 2002;91(3):339–347. [PubMed: 12022310]
15. Shah SS, Hall M, Goodman DM, et al. Off-label drug use in hospitalized children. *Arch Pediatr Adolesc Med* Mar;2007 161(3):282–290. [PubMed: 17339510]
16. Yoon EY, Davis MM, El-Essawi H, Cabana MD. FDA labeling status of pediatric medications. *Clinical Pediatrics* 2006;45(1):75–78. [PubMed: 16429220]
17. Hopwood NJ, Hintz RL, Gertner JM, et al. Growth response of children with non-growth-hormone deficiency and marked short stature during three years of growth hormone therapy. *J Pediatr* Aug; 1993 123(2):215–222. [PubMed: 8345416]
18. Cuttler L, Silvers JB, Singh J, et al. Short stature and growth hormone therapy. A national study of physician recommendation patterns. *JAMA* Aug 21;1996 276(7):531–537. [PubMed: 8709401]
19. August GP, Lippe BM, Blethen SL, et al. Growth hormone treatment in the United States: demographic and diagnostic features of 2331 children. *J Pediatr* Jun;1990 116(6):899–903. [PubMed: 2348293]
20. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics* Aug;2004 114(2 Suppl 4th Report):555–576. [PubMed: 15286277]
21. Thomson Micromedex Healthcare Series Volume 121. [Accessed August 26, 2004]. <http://micromedex.med.umich.edu/mdxcgi/mdxhtml.exe?&tmpl=mdxhome.tm1&SCRNAME=mdxhome&CTL=E:\mdx\mdxcgi\megat.sys>

22. U.S. FDA. Pediatric Exclusivity Labeling Changes. [Accessed January 1, 2006]. <http://www.fda.gov/cder/pediatric/labelchange.htm>

ABBREVIATIONS USED

ACE	Angiotensin Converting Enzyme
ADHD	Attention Deficit Hyperactivity Disorder
ARB	Angiotensin Receptor Blocker
Ca²⁺	Calcium
FDA	Food and Drug Administration
ICD-9	International Classification of Diseases, 9 th Revision

Table 1
Off-label Use of Antihypertensive Drugs*, by Class (n=3660)

Class of Antihypertensives	n	Proportion Off-label (%)
Ca ²⁺ channel blockers	530	100
ARBs [^]	80	78
ACE inhibitors	699	63
β-blockers	1740	42
Diuretics	611	12
All classes	3660	50

* Pertains to the index prescription claim; p<0.001

[^] ARBs denote Angiotensin Receptor Blockers

Table 2
Variation in Off-label Proportion by Class of Antihypertensives, Age Group and Gender* (n=3660)

	Ca ²⁺ channel blockers (n=530) n off-label (%)	[^] ARBs (n=80) n off-label (%)	ACE inhibitors (n=699) n off-label (%)	β-blockers (n =1740) n off-label (%)	Diuretics (n=611) n off-label (%)
Girls	18 (100)	1 (100)	30 (59)	14 (44)	2 (4)
≤5 years (n=152)	33 (100)	2 (50)	41 (56)	36 (27)	1 (4)
6–11 years (n=267)	237 (100)	13 (76)	107 (60)	345 (43)	34 (10)
≥12 years (n=1586)					
Boys	25 (100)	5 (100)	43 (69)	22 (54)	5 (7)
≤5 years (n=205)	48 (100)	5 (71)	35 (51)	57 (28)	9 (22)
6–11 years (n=364)	169 (100)	36 (78)	184 (69)	263 (50)	25 (33)
≥12 years (n=1086)					

* Pertains to the index prescription claim; p<0.001

[^] ARBs denote Angiotensin Receptor Blockers

Table 3
Results from Multivariate Logistic Regression Model of Off-label Use of Antihypertensive Drugs ¶ (n=3660)

	OR	95% CI
Male (compared to females)	1.43	1.22–1.68
Oldest age group (≥ 12 years) [±]		
Diuretics	1.00	Reference
ACE inhibitors	10.18	7.23–14.34
ARBs [^]	18.04	9.32–34.91
β -blockers	4.83	3.59–6.50
Ca ²⁺ channel blockers		
Middle age group (6–11 years)		
Diuretics	0.96	0.46–2.00
ACE inhibitors	0.67	0.29–1.54
ARBs [^]	0.54	0.11–2.54
β -blockers	0.44	0.20–0.97
Ca ²⁺ channel blockers		*
Youngest age group (≤ 5 years)		
Diuretics	0.32	0.14–0.73
ACE inhibitors	3.04	1.21–7.67
ARBs [^]		†
β -blockers	3.39	1.32–8.68
Ca ²⁺ channel blockers		*

¶ Odds ratios reflect the relative odds of off-label use of antihypertensive drugs controlling for patient age, gender, drug class, and age*drug class interaction term.

[±] The reference group for the age*drug class interaction is the oldest age group prescribed diuretics.

[^] ARBs denote Angiotensin Receptor Blockers

* All Ca²⁺ channel blockers for all age groups were off-label, thus the odds ratios were indeterminate.

† All ARBs for the youngest age group were off-label, thus the odds ratio was indeterminate.

Table 4
Mean Cost of Antihypertensive Drugs per Child per 30-day fill, by Class (n=3660)

Class of Antihypertensives	Off-label Mean Cost (95% CI), \$	On-label Mean Cost (95% CI), \$
Ca ²⁺ channel blockers	35.76 (32.60–38.93)	*
ARBs [^]	44.36 (41.26–47.46)	42.43 (37.04–47.81)
ACE inhibitors	25.73 (23.65–27.82)	26.01 (23.61–28.40)
β-blockers	12.71 (11.73–13.69)	18.95 (17.85–20.05)
Diuretics	12.06 (9.67–14.45)	20.82 (19.06–22.58)

* All Ca²⁺ channel blockers for all age groups were off-label.

[^] ARBs denote Angiotensin Receptor Blockers