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ORIGINAL REPORT

Stage 2 hypertension: predictors of failure to achieve blood pressure control and the impact of adding one additional antihypertensive class

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ABSTRACT

Background and objective Controlling blood pressure (BP) for patients with stage 2 hypertension remains challenging. This research aimed to: (i) identify predictors of failure to achieve BP control, (ii) determine the association of adding one additional antihypertensive class with achieving BP control, and (iii) describe the prescribed antihypertensive regimens.

Methods Electronic medical record data from 25 multi-specialty medical groups in the USA were used. The study cohort included patients with stage 2 hypertension in 2012. BP control rates were determined at 6 months from the date of the stage 2 BP. Using multivariable logistic regression and validation by Monte Carlo simulation, we determined independent baseline predictors of not achieving BP control (<140/90).

Results Included were 107 903 patients. Baseline predictors of failure to achieve BP control included the following: a prior stage 2 BP, systolic BP ≥ 165, Black race, male sex, income ≤ $35 000, body mass index ≥ 30, age ≥ 65 years, and no office visits. Increasing from single-class to dual-class antihypertensive therapy was associated with a 42% increased odds of achieving BP control (odds ratio 1.42; 95% CI 1.22, 1.64); however, this effect was attenuated as the number of baseline antihypertensive classes increased. The 10 most frequently prescribed regimens accounted for only 40% of all antihypertensive regimens.

Conclusions Among patients with stage 2 hypertension, a prior stage 2 BP, a systolic BP ≥ 165, and fewer office visits were strong predictors of failure to achieve BP control. Increasing to dual-class antihypertensive therapy was significantly associated with achieving BP control. There is broad heterogeneity in the antihypertensive regimens prescribed. Copyright © 2015 John Wiley & Sons, Ltd.

KEY WORDS—stage 2 hypertension; predictive model; dual-class antihypertensive therapy; encounter frequency; blood pressure control; pharmacoepidemiology

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INTRODUCTION

The risk of cerebrovascular disease, myocardial infarction, chronic kidney disease (CKD), and mortality is magnified as blood pressure increases.[1–6] Recent studies have shown that patients with stage 2 hypertension (systolic blood pressure (SBP) ≥ 160 or diastolic blood pressure (DBP) ≥ 100) have about twice the risk of mortality, renal failure, and stroke, compared to patients with stage 1 hypertension (SBP ≥ 140 and <160 or DBP ≥ 90 and <100).[2,5] Achieving blood pressure (BP) control is critical to improving clinical outcomes in these high-risk patients.

Stage 2 hypertension is a common (10–20% of patients with hypertension) and serious condition, which motivated consensus panels to develop treatment guidelines to assist health care providers (HCPs) in making evidence-based decisions.[7–11] Yet, HCPs struggle to achieve BP control among their patients with stage 2 hypertension. A recent study found only 50% of patients with incident stage 2 hypertension achieved BP control. Risk factors for not achieving control included higher body mass index (BMI), higher baseline SBP, CKD, and

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diabetes. Strikingly, only 50% of patients were treated according to hypertension guidelines.[12–14]

Hypertension guidelines emphasize the importance of pharmacotherapy for stage 2 hypertension and consistently recommend at least dual-class antihypertensive therapy.[11,15] Research also supports the benefits of adding a third antihypertensive class for those who are inadequately controlled with dual-class therapy.[16] Antihypertensive therapy is not the only intervention associated with achieving BP control. In a study of patients with stage 1 hypertension and diabetes mellitus, more frequent health care provider interactions were associated with more rapid normalization of blood pressure. However, it was not clear if these findings would hold true for patients with stage 2 hypertension.[17]

The focus on stage 2 hypertension was meant to yield results applicable to patients at the greatest risk for serious complications and for whom achieving BP control is most challenging. This study had three specific aims: to determine baseline predictors of failure to achieve blood pressure control (aim 1 (primary)), to determine the association of achieving BP control with adding one additional antihypertensive class to the baseline antihypertensive regimen (aim 2), and to describe the prescribed antihypertensive regimens (aim 3).

METHODS

Study design

A retrospective cohort study was conducted to evaluate baseline predictors associated with failure to achieve BP control among patients with stage 2 hypertension (aim 1).

Data source

The study population was extracted from the Humedica electronic medical record (EMR) database. This normalized, statistically de-identified EMR database includes demographics (e.g., age, sex, and race), medical conditions classified using International Classification of Diseases, Ninth Edition, Clinical Modification codes, vital signs and clinical characteristics (e.g., BP, height, and weight), laboratory test dates and results, pharmacotherapy prescribed, health care utilization metrics (e.g., ambulatory office visits and procedures performed), insurance type (e.g., Medicare and commercial), and imputed median household income (based on census data).

These data provide a retrospective, longitudinal view of patients who received care from 25 multi-specialty medical groups across the USA, ranging in size from approximately 100 to over 3000 physicians. The medical groups contributing data participate in the American Medical Group Association's Anceta learning collaborative, which is conducted in partnership with Humedica, an Optum company.

Study population

The study population included patients with stage 2 hypertension in 2012 whose BP was measured during routine clinical care as part of an ambulatory evaluation and management office visit (referred to as office visit) with an HCP (physicians and advanced practice providers). We included office visits, which fell into the following Berenson-Eggers Type of Service (BETOS) categories: M1A (new patient), M1B (established patient), M5D (certain specialist visits), or M6 (other consultations). We included patients that met either of the two following criteria: (criterion 1) two stage 2 BPs on different days in 2012, but within 182 days of one another, or (criterion 2) a single stage 2 BP in 2012 with a prescribing record for an antihypertensive agent within 30 days. The index date was the date of the second stage 2 BP (for criterion 1) or the date of the single stage 2 BP (for criterion 2). If more than one BP measurement was recorded on a given day, the lowest SBP and lowest DBP on the day were used.

Study cohort: inclusion and exclusion criteria

Patients with stage 2 hypertension were included in the study cohort if they met *all* of the following inclusion criteria: (i) identifiable gender; (ii) age $\geq$40 and $\leq$85 years at the index date; (iii) a 12-month baseline period prior to the index date; (iv) a 6-month follow-up BP measurement; and (v) pre-baseline EMR 'activity' (activity was classified by evidence of an office visit, a diagnosis code, a procedure code, a BP measurement, a laboratory test, or a medication prescribing record) (Figure 1).

Patients with *any* of the following prior to the index date were excluded from the study cohort: (i) secondary hypertension or another condition indicating secondary hypertension; (ii) pregnancy-related hypertension; (iii) three or more prednisone prescribing records during the baseline period; (iv) stage 5 CKD or end-stage renal disease; or (v) an estimated glomerular filtration rate < 15 mL/minute per 1.73 m^2. The Mayo Clinic quadratic equation was used to determine the estimated glomerular filtration rate, based on measured serum creatinine. The attrition table is provided in eFigure 1 (available in Supporting Information).

Outcome classification (aims 1 and 2)

The outcome for aim 1 was classified as failure to achieve BP control at approximately 6 months

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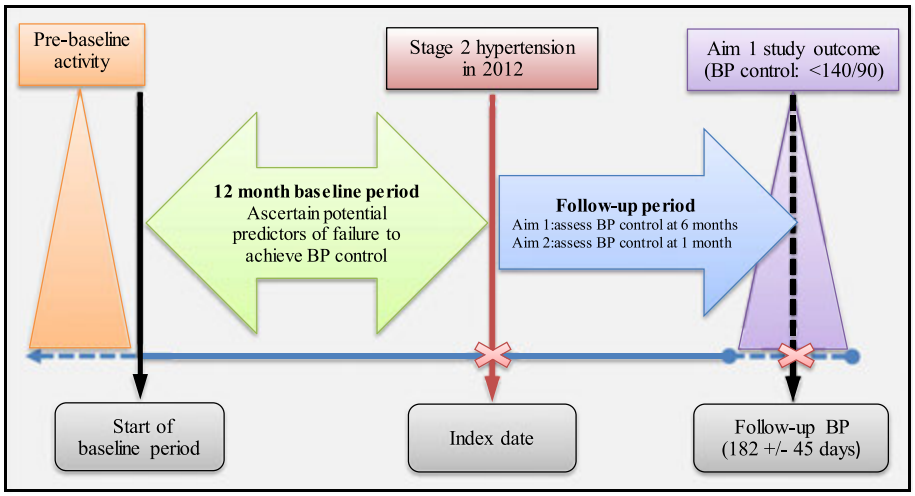

Figure 1. Study schema. BP, blood pressure

(182 ± 45 days) following the index date. BP control was classified as SBP < 140 and DBP < 90. The outcome for aim 2 was classified as achieving BP control within 30 days following the index date. All BP measurements occurred during an ambulatory office visit. If there was more than one BP measurement during each follow-up period, the BP measurement nearest to the follow-up date was used. BPs were recorded by a health care professional using a manual BP cuff, with the patient seated.

Baseline candidate predictor variable classification (aim 1)

All baseline candidate predictor variables (CPVs) were ascertained from the EMR database. The CPVs included the following: demographics (e.g., sex and race), clinical measures (e.g., BMI and baseline BP measurements), comorbidities, prescribed medications, health care utilization factors (e.g., number of office visits), insurance type, and median household income. Demographics were classified on the index date. Clinical measures were classified during the 12-month baseline period and on the index date. Comorbidities were classified by the presence of at least one diagnosis code during the baseline period, including the index date. Health care utilization factors (e.g., the number of office visits) and prescribed medications were classified during the baseline period. Median household income (referred to as income) was imputed from US Census data using the patient's five-digit zip code of residence on the index date. If the patient zip code was not available, the zip code for the affiliated medical group was used. In addition to the CPVs presented in Table 1, other CPVs were also evaluated (see eTable 1 for a listing of additional CPVs).

Exposure classification (aim 2)

We classified antihypertensive agents at the class level (e.g., angiotensin-converting enzyme (ACE) inhibitor or thiazide diuretic). The specific antihypertensive classes are listed at the bottom of Table 1. For aim 2, we compared patients who were prescribed one additional antihypertensive agent on the index date (the "exposed" group) to patients whose prescribed antihypertensive regimen was exactly the same during the baseline period and on the index date (the "unexposed group"). The baseline and index date antihypertensive regimens were classified by the number of distinct antihypertensive classes prescribed. The antihypertensive regimens were classified during the 12-month baseline period and separately on the index date.

Patients were classified as "unexposed" who were prescribed the exact same antihypertensive regimen during the baseline period and on the index date. For example, patients would be classified as "unexposed" if they were prescribed an ACE inhibitor and a thiazide diuretic during the baseline period and an ACE inhibitor and a thiazide diuretic on the index date. Using the same methodology, patients were considered "exposed" who were prescribed one additional antihypertensive agent on the index date compared with the prescribed baseline antihypertensive regimen. Like the "unexposed" group, the number of antihypertensive classes and the specific agents remained the same (during the baseline period and on the index date) except for the prescribing of one additional

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Table 1. Study population characteristics stratified by BP control at the 6-month follow-up BP measurement date

Study population characteristics stratified by hypertension control during 6-month follow-up	Total		BP < 140/90		BP ≥ 140/90	
	107 903		53 003	49.1%	54 900	50.9%
Demographics						
Age: mean, SD	64.9	11.8	65.0	11.7	64.7	11.8
Sex: female	63 657	59.0%	31 757	59.9%	31 900	58.1%
Black or African American	16 673	15.5%	7 236	13.7%	9 437	17.2%
Income: <$35 000	31 072	28.8%	14 482	27.3%	16 590	30.2%
Medicare	51 243	47.5%	24 854	46.9%	26 389	48.1%
Clinical measures (during the baseline period or on the index date)						
Systolic BP at index: mean, SD	165.2	13.8	163.8	13.5	166.5	14.0
Diastolic BP at index: mean, SD	89.5	13.0	89.4	12.8	89.5	13.2
BP ≥ 160/100 during baseline	30 216	28.0%	11 406	21.5%	18 810	34.3%
BMI ≥ 30	60 889	56.4%	29 510	55.7%	31 379	57.2%
Comorbidities (during the baseline period)						
Dyslipidemia	68 710	63.7%	34 230	64.6%	34 480	62.8%
Type 2 diabetes	35 927	33.3%	17 140	32.3%	18 787	34.2%
Depression	17 442	16.2%	9 365	17.7%	8 077	14.7%
Coronary artery disease	13 951	12.9%	7 292	13.8%	6 659	12.1%
Peripheral vascular disease	11 232	10.4%	5 919	11.2%	5 313	9.7%
Arrhythmia	10 528	9.8%	5 537	10.4%	4 991	9.1%
Chronic obstructive pulmonary disease (COPD)	10 224	9.5%	5 343	10.1%	4 881	8.9%
Chronic kidney disease (CKD)	10 220	9.5%	4 956	9.4%	5 264	9.6%
Cerebrovascular disease	10 044	9.3%	5 177	9.8%	4 867	8.9%
Atrial fibrillation (A-fib)	9 150	8.5%	4 814	9.1%	4 336	7.9%
Congestive heart failure (CHF)	6 894	6.4%	3 541	6.7%	3 353	6.1%
Myocardial infarction	4 155	3.9%	2 164	4.1%	1 991	3.6%
Health care utilization (during the baseline period and 6-month follow-up period)						
≥1 Hospital admission during baseline	17 782	16.5%	9 159	17.3%	8 623	15.7%
≥1 Emergency Department visit during baseline	21 379	19.8%	10 818	20.4%	10 561	19.2%
No. of baseline office visits: mean, SD	5.8	5.9	6.1	6.1	5.6	5.6
No. of follow-up office visits: mean, SD	5.8	4.0	6.1	4.2	5.5	3.8
Non-antihypertensive medications (during the baseline period)						
Number of medications: mean, SD	4.1	2.9	4.2	3.0	3.9	2.9
Antihypertensive medications (during the baseline period)						
Number of RxAH classes*						
0	24 019	22.3%	11 836	22.3%	12 183	22.2%
1	20 795	19.3%	10 475	19.8%	10 320	18.8%
2	24 295	22.5%	12 257	23.1%	12 038	21.9%
3	19 262	17.9%	9 391	17.7%	9 871	18.0%
4+	19 532	18.1%	9 044	17.1%	10 488	19.1%
Antihypertensive medications (During the 6-month follow-up period)						
Number of RxAH classes						
0	10 120	9.4%	4 269	8.1%	5 851	10.7%
1	26 070	24.2%	12 942	24.4%	13 128	23.9%
2	30 048	27.8%	15 266	28.8%	14 782	26.9%
3	21 733	20.1%	10 727	20.2%	11 006	20.0%
4+	19 932	18.5%	9 799	18.5%	10 133	18.5%
One additional antihypertensive class†	22 570	20.9%	11 787	22.2%	10 783	19.6%
Blood pressure at the 6-month follow-up BP measurement						
Stage 2 (≥160/100)	18 821	17.4%	—	—	—	—
Stage 1 (SBP 140–159 or DBP 90–99)	36 079	33.4%	—	—	—	—

BP, blood pressure; SD, standard deviation; BMI, body mass index; SBP, systolic BP; DBP, diastolic BP.

*We classified antihypertensive agents into the following classes: angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, thiazide diuretics (thiazide), potassium sparring diuretics (k+), loop diuretics (loop), calcium channel blockers—centrally acting, calcium channel blockers—other (e.g., dihydropyridines), direct renin inhibitors, alpha beta blockers, beta blockers, selective anti-adrenergic receptor antagonist, centrally acting anti-adrenergic, peripherally acting anti-adrenergic, vasodilators, and other (e.g., reserpine, diazoxide, and mecamylamine).

†To classify the addition of one antihypertensive class, we calculated the difference between the number of prescribed follow-up antihypertensive classes and the number of prescribed baseline antihypertensive classes.

antihypertensive agent on the index date. For example, patients would be classified as "exposed" if they were prescribed an ACE inhibitor and a thiazide diuretic during the baseline period and an ACE inhibitor, a thiazide diuretic, and a beta blocker on the index date. To retain the internal validity of the aim 2 analyses, patients who were prescribed more than one additional antihypertensive agent on the index date (compared

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with the baseline antihypertensive regimen) were not included in the aim 2 analyses. We also did not analyze patients who were prescribed different antihypertensive agents during the baseline period and on the index date (e.g., ACE inhibitor (baseline); angiotensin receptor blockers and thiazide diuretic (index date)). Additionally, because the aim 2 outcome (achieving BP control) was classified within 30 days following the index date, we only analyzed patients who were prescribed an antihypertensive on the index date (with the exception of the "unexposed" group who were not prescribed an antihypertensive agent during the baseline period nor on the index date—these patients were included as the reference group for those who initiated single-class antihypertensive therapy on the index date).

Antihypertensive regimens prescribed (aim 3)

We classified the specific antihypertensive regimens prescribed (at the antihypertensive class level) from the index date to the 6-month follow-up date.

Statistical analysis (aim 1)

The seven step statistical method used to build the predictive model for aim 1 is provided in the Supporting Information (eTable 2). In summary, baseline predictors of failure to achieve BP control were determined by univariate analyses of all CPVs and multivariable logistic regression (using the likelihood ratio test) and validated by Monte Carlo bootstrap simulation. As described in the Supporting Information, collinearity of each pairwise combination of the significant predictor variables was assessed. When collinearity was identified (Pearson correlation coefficient<-0.8 or >0.8), we retained the variable more significantly associated with the dependent variable (failure to achieve BP control). CPVs included in the multivariable model (using the likelihood ratio test ($p<0.05$)) as well as those included in ≥80% of the bootstrap simulated models were retained in the final predictive model.

Statistical analysis (aim 2)

We determined the association (odds ratio and 95% confidence interval) of adding one additional antihypertensive class (on the index date) with achieving BP control (BP < 140/90) within 30 days following the index date—stratified by the number of prescribed antihypertensive classes in the baseline regimen. For stratification purposes, we categorized the number of prescribed baseline antihypertensive classes as 0, 1, 2, 3, and 4+. Five separate multivariable logistic regression models were developed (one for each stratum). The stratum-specific multivariable models were adjusted for significant baseline predictors (from aim 1) and confounders, which changed the unadjusted (crude) association (odds ratio) by ≥20%. We evaluated, as potential confounders, the variables listed in Table 1 and eTable 1.

Secondary analyses

We re-evaluated aim 1 using the same methodology as previously described, but used a 12-month rather than a 6-month follow-up period. We also stratified the aim 1 analyses by the following: (i) patients with prevalent versus incident stage 2 hypertension, (ii) patients who were prescribed and not prescribed an antihypertensive agent during the baseline period, and (iii) patients who entered the cohort by two stage 2 BPs versus one stage 2 BP and an antihypertensive agent within 30 days. We also describe the proportion of study cohort members who, contrary to hypertension guidelines for stage 2 hypertension, were not prescribed at least dual-class antihypertensive therapy during the 6-month follow-up period.

RESULTS

There were 107,903 patients with stage 2 hypertension in the study cohort. At the 6-month follow-up BP measurement date, 49.1% achieved BP control (BP < 140/90), 33.4% improved to stage 1 hypertension, and 17.4% continued to have stage 2 hypertension. Stratified by BP control status at 6 months, Table 1 shows the distribution of demographics, hypertension characteristics, comorbidities, procedures, pharmacotherapy, and patient surveillance factors. The average age (standard deviation (SD)) for all study cohort members was 64.9 (11.8) years, and 59.0% were female. The average SBP (SD) and DBP (SD), on the index date, were 165.2 (13.8) and 89.5 (13), respectively. Most patients (68%) entered the study cohort because of an isolated stage 2 SBP (SBP ≥ 160) rather than a stage 2 DBP; 15% had both. The percentage of patients with BMI ≥ 30 was 56.4%. The percentages with diabetes mellitus, CKD, and congestive heart failure were 33.3%, 9.5%, and 6.4%, respectively. Regarding baseline antihypertensives, 77.7% were prescribed an antihypertensive agent during baseline, and 54% were prescribed two or more different antihypertensive classes.

Figure 2 shows the significant, independent baseline predictors of failure to achieve BP control at 6 months. The odds ratios are adjusted only for the other

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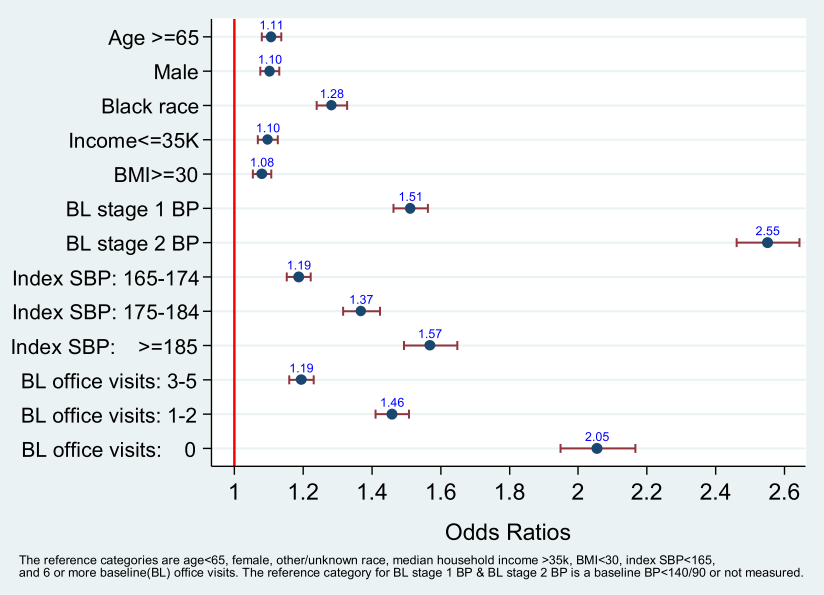

Figure 2. Predictors of failure to achieve blood pressure (BP) control at 6 months following the index date. The predictors were classified during the 12-month baseline (BL) period or on the index date. BMI, body mass index; SBP, systolic blood pressure

significant, independent predictors shown in the figure. The strongest predictor of failure to achieve BP control was having a stage 2 BP during the baseline period (reference category was having controlled BP (<140/90) at all readings during the baseline period). Accounting for the other predictors in the model, patients with a prior stage 2 BP (within 12 months prior to the index date) were 2.5 times more likely to not achieve BP control. The next most significant predictor was a four-level categorical variable representing the number of ambulatory office visits during the baseline period. This variable (baseline office visits) was categorized as ≥6 baseline office visits (the reference category), 3–5, 1–2, and 0. Patients with zero baseline office visits were more than twice as likely to not achieve BP control compared with patients with ≥6 baseline office visits. Another important predictor was a four-level categorical variable representing different levels of SBP on the index date. This variable (index SBP) was categorized as index SBP <165 (the reference category); ≥165 index SBP <175; ≥175 index SBP <185; and index SBP ≥185. Patients with a SBP ≥185 on the index date were the least likely to achieve BP control. Other predictors of not achieving BP control included Black race compared with all other races, male sex, income≤$35 000, BMI≥30, and age≥65 years.

Figure 3 depicts the association of adding one additional antihypertensive class (to the baseline antihypertensive regimen) with achieving BP control within 30 days following the index date—stratified by the number of prescribed baseline antihypertensive classes (0, 1, 2, 3, and 4+). The "unexposed" group, for each stratum, includes patients whose prescribed antihypertensive regimen was exactly the same during the baseline period as was prescribed on the index date. Among patients who were prescribed one antihypertensive class during the baseline period, transitioning to dual-class antihypertensive therapy (i.e., two prescribed antihypertensive classes) was associated with a 42% (odds ratio 1.42 95% confidence interval: 1.54–1.77) increased likelihood of achieving BP control compared with patients who were prescribed only one antihypertensive agent during the baseline period and on the index date. However, the strength of the association between adding one antihypertensive medication and achieving BP control diminished incrementally as the number of prescribed baseline antihypertensive classes increased.

For aim 3, there were a total of 2607 different combinations of antihypertensive classes prescribed during the 6-month follow-up period. Table 2 shows the 10 most commonly prescribed regimens accounted for only 40% of all prescribed antihypertensive regimens. It is important to note that five of the top 10 regimens were single-class antihypertensive therapy.

Secondary analyses

For aim 1, the predictors of failure to achieve BP control at 6 months following the index date were mostly

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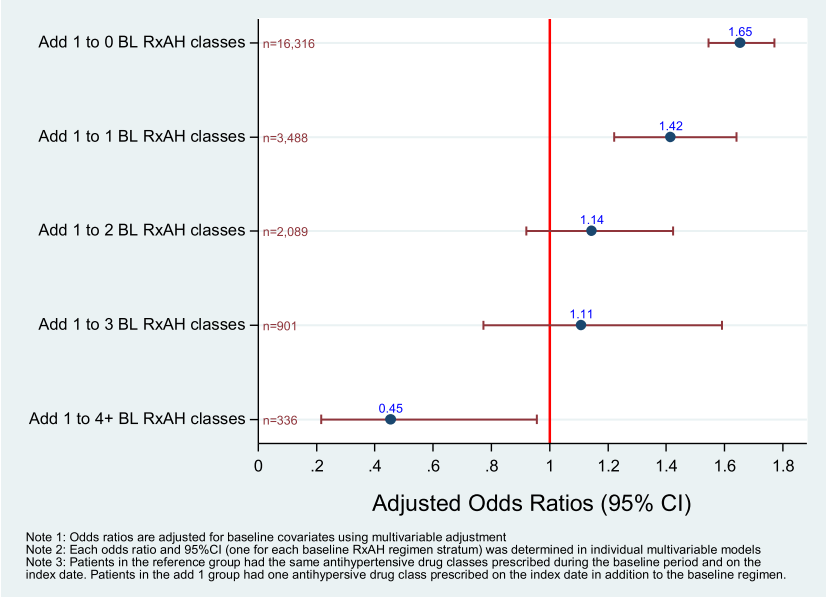

Figure 3. Association (adjusted odds ratios and 95% confidence interval (CI)) between adding one antihypertensive class (RxAH) on the index date to the baseline (BL) antihypertensive regimen and achieving blood pressure control at 30 days—stratified by the number of baseline antihypertensive classes. The sample size for each stratum is on the inside of the *y*-axis

Table 2. Top 10 antihypertensive regimens prescribed in the 6-month follow-up period among patients prescribed at least one antihypertensive

Follow-up antihypertensive regimens	% of patients
ACE	8.1
ACE + thiazide	5.9
BB	5.5
CCB	3.4
ARB + thiazide	3.2
ARB	3.2
ACE + BB	3.1
ACE + CCB	2.6
Thiazide	2.5
ACE + thiazide + BB	2.5
Other antihypertensive regimen	60.0

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; thiazide, thiazide diuretics; CCB, calcium channel blockers-dihydropyridines; BB, beta blockers.

consistent at 12 months following the index date; however, age was no longer a significant predictor (data not presented). At 12 months, 51% of patients achieved BP control; however, only 32% of patients achieved BP control at both 6 and 12 months.

eTable 3 shows the proportion of patients prescribed 1, 2, 3, and 4+ antihypertensive classes during the 6-month follow-up period. Contrary to the hypertension guideline recommendations, 26.7% of study cohort members with stage 2 hypertension, who were prescribed an antihypertensive during follow-up, were prescribed only one antihypertensive class.

The additional aim 1 secondary analyses are presented in eTable 4. Individual predictive models were developed for each stratum. For the most part, these secondary analyses depict the robustness of the results from the primary aim 1 analysis. While the odds ratios are somewhat attenuated in certain strata (perhaps due to reduced precision from smaller sample sizes), the predictors of failure to achieve BP control were consistent. No additional predictors of failure to achieve BP control were identified in these models. In each stratum evaluated, having a prior stage 2 BP (within 12 months prior to the index date) and an index SBP ≥185 were strongly associated with failure to achieve BP control. Among patients with incident stage 2 BP (no baseline BP measurement) and those with no baseline prescribing record for an antihypertensive, the number of baseline office visits was no longer significantly predictive of failure to achieve BP control.

DISCUSSION

Consistent with previous research, ~50% of patients with stage 2 hypertension achieved blood pressure control.[12,18] Our study also confirms and extends upon prior research by identifying predictors of failure to achieve BP control specifically for patients with stage 2 hypertension. The goal of the predictive model was to give HCPs a tool to identify patient characteristics associated

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with the greatest risk of not achieving BP control and ultimately patients, who possess these characteristics, who are at the highest risk for deleterious outcomes (e.g., stroke, myocardial infarction (MI), renal dysfunction, and death). The strongest predictor of not achieving BP control was having a stage 2 BP in the year before the index date. These patients were ~2.5 times as likely not to achieve BP control compared with patients with normal baseline BP (i.e., BP < 140/90). Another robust predictor of not achieving BP control was the SBP on the index date (index SBP). Compared with patients with an index SBP <165, those with an index SBP ≥185 were ~57% more likely not to achieve BP control at 6 months. An important health care utilization metric that was predictive of failure to achieve BP control was the number of baseline office visits. Our results showed that patients with no baseline office visits were twice as likely to not achieve BP control compared with patients with an office visit at least every other month. Given the potential implications of persistently uncontrolled stage 2 hypertension, this frequency of patient–provider encounters is well justified. Other predictors included Black race compared with other races, male sex, and obesity (BMI ≥ 30). Not reported in other studies was the association of income—which may be related to access to health care; however, further research is warranted to elucidate this association.

These findings are consistent with previous research, although other studies, not restricted to stage 2 hypertension, also found diabetes, CKD, and cardiovascular disease predictive of failure to achieve BP control.[13,14] Previous studies in patients with relatively mild hypertension found that increased patient–provider encounters are associated with an increased likelihood of achieving BP control.[17] Our findings show that, among patients with stage 2 hypertension, the frequency of baseline patient–provider encounters were strongly associated with failure to achieve BP control. These results are supported by prior researchers who reported faster BP normalization with shorter intervals between provider–patient encounters.[17,19]

As expected, adding one additional antihypertensive class (to the prescribed baseline antihypertensive regimen) was associated with an increased likelihood of achieving BP control. However, the more antihypertensive classes a patient was already prescribed during baseline resulted in a smaller incremental benefit. Once patients were already prescribed two or more baseline antihypertensive classes, the association was no longer significant. These results are mostly consistent with prior research except that adding a third antihypertensive class (to patients on dual-class antihypertensive therapy during baseline) was not significantly associated with achieving BP control. This may be related to reduced precision arising from the smaller sample size in that stratum ($n = 2089$).

We found substantial heterogeneity in the prescribed antihypertensive regimens during the 6-month follow-up period. Five of the top 10 antihypertensive regimens included only a single-class antihypertensive therapy. The top 10 antihypertensive regimens accounted for only 40% of all regimens prescribed. This degree of heterogeneity may be related to patient comorbidities, lack of antihypertensive efficacy, side effects of certain antihypertensives, numerous antihypertensives available, or perhaps a lack of comparative effectiveness data to guide prescribing decisions. Further research is warranted to better understand the antihypertensive prescribing heterogeneity for patients with stage 2 hypertension.

It is encouraging that, consistent with the recommendations of antihypertensive guidelines, ~73% of patients with stage 2 hypertension were prescribed at least dual-class antihypertensive therapy (within 6 months following the index date). This percentage is more than three times higher than reported in a 2008 study, using a US-based EMR database, which showed 24% of patients were prescribed at least two antihypertensive classes.[18] The difference may be attributable to heterogeneous practice patterns among the providers included or perhaps increased awareness of the effectiveness of dual-class or combination antihypertensive therapy over time.

The findings from this study are likely generalizable to patients with stage 2 hypertension in the USA and other countries with similar age, race, comorbidity distributions, and health care structure. A benefit of using EMR data from multiple multi-specialty medical groups is the diversity of health plans included, which may provide a study cohort more representative of patients receiving ambulatory care in the USA. Supporting the generalizability of the study findings, (i) the baseline characteristics were similar for patients with stage 2 hypertension who were included versus excluded from study entry, and (ii) the primary findings were consistent for patients who were prescribed an antihypertensive agent in the baseline period and those who were not.

For aim 2, a potential misclassification relates to classifying medication exposure based on prescribing data rather than pharmacy dispensing data. In the absence of complete administrative claims data, it is possible that patients with an antihypertensive prescribing record in the EMR never filled the medication at the

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pharmacy. This would potentially bias the aim 2 findings. However, given that both exposed and unexposed groups had an antihypertensive prescribing record on the index date (except the reference or "unexposed" group who were not prescribed an antihypertensive agent during baseline nor on the index date), it is likely that any misclassification related to not filling a prescription would be non-differential between the exposure groups and attenuate the association toward the null. Further research, using linked clinical and pharmacy claims data, is warranted to confirm the associations found in this study (for aim 2). Furthermore, it is possible that study cohort members received medical care, including antihypertensive treatment, outside the EMR ascertainment network. We mitigated this bias to some degree by requiring that most patients included in the aim 2 analyses had evidence of an antihypertensive prescribing record on the index date. Finally, like any observational study, this study is exposed to potential confounding bias. We adjusted for confounding using multivariable adjustment; however, it was not possible to adjust for variables that could not be identified or measured. Including predictors of blood pressure control from prior research, we assessed all variables as potential confounders and adjusted for true confounders in the multivariable logistic regression models.

CONCLUSIONS

Controlling BP for patients with stage 2 hypertension remains challenging. The most significant baseline predictors of failure to achieve BP control were having a prior stage 2 BP, an SBP $\geq$ 185, and no office visits in the last 12 months. Adding one additional antihypertensive agent was associated with an increased likelihood of achieving BP control; however, the magnitude of the effect diminished as the number of baseline classes increased. There is broad heterogeneity in the antihypertensive regimens prescribed. Contrary to hypertension guidelines, ~27% of patients with stage 2 hypertension were prescribed single-class antihypertensive therapy as opposed to the recommended dual-class antihypertensive therapy.

CONFLICT OF INTEREST

The authors declare no conflict of interest. The authors were employed by AMGA/Anceta or their previously mentioned institutions during the conduct of this study (study design to manuscript development).

KEY POINTS

Among patients with stage 2 hypertension:

- 50% achieved BP control at six months.
- Significant, independent predictors of failure to achieve BP control were: prevalent stage 2 hypertension, a SBP > 185, and fewer baseline office visits.
- Intensifying from single-class to dual-class antihypertensive therapy significantly increased the likelihood of achieving BP control (OR=1.42).
- There is broad heterogeneity in the antihypertensive regimens prescribed.
- Contrary to hypertension guidelines, 27% were prescribed single-class antihypertensive therapy.

ETHICS STATEMENT

This retrospective, observational database study presents no more than minimal risk of harm to patients. All study data were accessed in compliance with data use principles agreed to by the participating medical groups and in accordance with HIPAA and applicable state and federal laws governing the privacy and security of health information and personal data. This retrospective database study is not classified as research involving human subjects (under 45 CFR 46.101) for the following reasons: (i) there was no interaction with human subjects, (ii) all data were collected during routine clinical practice prior to study initiation (no additional data were collected during the study), and (iii) all study data were de-identified and no patient identifiers were available to the study investigators.

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NOVELTY AND SIGNIFICANCE

While prior research has been focused on hypertension in general, the focus on stage 2 hypertension was

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meant to yield results applicable to the patients at the greatest risk for serious complications and for whom achieving BP control is most challenging. This research provides a substantial contribution to improving population health as it offers guidance to health care providers about patient characteristics associated with failure to achieve BP control in the face of stage 2 hypertension and interventions that may help.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web site.

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