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Hypertension Treatment in Patients Receiving Ibrutinib: A Multicenter Retrospective Study

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Abstract:
Although Bruton's tyrosine kinase inhibitors (BTKis) are generally well-tolerated and less toxic than chemotherapy alternatives used to treat lymphoid malignancies, BTKis like ibrutinib have the potential to cause new or worsening hypertension (HTN). Little is known about the optimal treatment of BTKi-associated HTN. Randomly selected patients with lymphoid malignancies on a BTKi and anti-hypertensive drug(s) and with at least 3 months of follow up data were sorted into two groups: those diagnosed with HTN prior to BTKi initiation (prior-HTN), and those diagnosed with HTN after BTKi initiation (de novo HTN). Generalized estimating equations assessed associations between time varying mean arterial pressures (MAPs) and individual anti-HTN drug categories. Of the 196 patients included in the study, 118 had prior-HTN, and 78 developed de novo HTN. Statistically significant mean MAP reductions were observed in patients with prior-HTN who took beta blockers (BBs) with hydrochlorothiazide (HCTZ), (-5.05 mmHg; 95% CI -10.0 to -0.0596; p = 0.047), and patients diagnosed with de novo HTN who took either an angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) with HCTZ (-5.47 mmHg; 95% CI -10.9 to -0.001; p = 0.05). These regimens also correlated with the greatest percentages of normotensive MAPs. Treatment of HTN in patients taking a BTKi is challenging and may require multiple anti-hypertensives. Patients with prior-HTN appear to benefit from combination regimens with BBs and HCTZ, whereas patients with de novo HTN appear to benefit from ACEi/ARBs with HCTZ. These results should be confirmed in prospective studies.

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Abstract

Although Bruton's tyrosine kinase inhibitors (BTKis) are generally well-tolerated and less toxic than chemotherapy alternatives used to treat lymphoid malignancies, BTKis like ibrutinib have the potential to cause new or worsening hypertension (HTN). Little is known about the optimal treatment of BTKi-associated HTN. Randomly selected patients with lymphoid malignancies on a BTKi and anti-hypertensive drug(s) and with at least 3 months of follow up data were sorted into two groups: those diagnosed with HTN prior to BTKi initiation (prior-HTN), and those diagnosed with HTN after BTKi initiation (de novo HTN). Generalized estimating equations assessed associations between time varying mean arterial pressures (MAPs) and individual anti-HTN drug categories. Of the 196 patients included in the study, 118 had prior-HTN, and 78 developed de novo HTN. Statistically significant mean MAP reductions were observed in patients with prior-HTN who took beta blockers (BBs) with hydrochlorothiazide (HCTZ), (-5.05 mmHg; 95% CI -10.0 to -0.0596; p = 0.047), and patients diagnosed with de novo HTN who took either an angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) with HCTZ (-5.47 mmHg; 95% CI -10.9 to -0.001; p = 0.05). These regimens also correlated with the greatest percentages of normotensive MAPs. Treatment of HTN in patients taking a BTKi is challenging and may require multiple anti-hypertensives. Patients with prior-HTN appear to benefit from combination regimens with BBs and HCTZ, whereas patients with de novo HTN appear to benefit from ACEi/ARBs with HCTZ. These results should be confirmed in prospective studies.

Key Points

- Patients treated for hypertension while taking ibrutinib benefit from combination therapy.

- Regimens that combine HCTZ and beta blockers benefit patients with prior-HTN, while HCTZ and ACEi/ARBs benefit patients with de novo HTN.

Introduction

Bruton tyrosine kinase inhibitors (BTKis) fulfill a critical role in the treatment of numerous lymphoid malignancies, including chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), Waldenström Macroglobulinemia (WM), and a subset of patients with diffuse large B-cell lymphoma (DLBCL).[1-9] For all indications, BTKis are administered with the hope of providing long-term disease control with limited toxicity, although prolonged exposure confers a legitimate risk of adverse events (AEs).[10] Hypertension (HTN) is a widely recognized adverse effect of BTKi use that often occurs late in the span of therapy and has the potential to cause major adverse cardiovascular events (MACEs) if not treated appropriately.[11-15] While standard antihypertensive (anti-HTN) medications are commonly employed to treat HTN in patients taking a BTKi, guidance on the optimal class of anti-HTN medication is lacking with some experts suggesting these drugs should be chosen according to patients' comorbidities or so as to avoid pharmacokinetic interactions between medications.[16,17]

Ibrutinib was the first covalent inhibitor of Bruton's tyrosine kinase to be approved for the treatment of patients with CLL, WM, MZL, and MCL. Its widespread use was accompanied by real-world experience with drug associated HTN, corroborated by data from both clinical trials and retrospective studies. New or worsened hypertension was identified in 78.3% of ibrutinib users over a median of 30 months in a series of 562 patients treated between 2009 and 2016. This same study reported high grade HTN (blood pressure > 160/100 mm Hg) in 17.7% of patients who were diagnosed with de novo HTN following BTKi initiation[14] Roeker and colleagues examined blood pressure data in 247 patients on ibrutinib and found that incident hypertension occurred in 34.8% of patients, while 49.5% of patients with pre-existing hypertension experienced ≥ grade 3 systolic hypertension.[18] Of these patients with HTN prior to starting ibrutinib, 20.6% had a change in their cardiovascular medication regimen in the first year after ibrutinib exposure. The median time to peak blood pressure (BP) was 6 months, suggesting a need for ongoing BP monitoring.

Data from clinical trials has reported smaller numbers of patients with new or worsening HTN on ibrutinib, although pooled analyses suggest it is a real problem. Long-term follow-up of the phase 3 RESONATE trial comparing ibrutinib with ofatumumab in patients with CLL found grade ≥ 3 HTN in only 4-9% of patients over the first four years of treatment.[1] In contrast, extensive follow-up data from the phase 1b/11 PCYC-1102 study reported grade ≥ 3 HTN in 28% of patients.[19] To better understand the association between ibrutinib and HTN, Caldeira et al. conducted a meta-analysis of eight randomized controlled trials (including RESONATE and RESONATE-2) to show that ibrutinib is associated with an increased risk of HTN as demonstrated by a risk ratio of 2.82 (95%CI 1.52-5.23; p-value <0.001).[13]

Although plenty of data corroborate a relationship between BTKis and HTN, there are no formal guidelines on how to optimize the treatment of patients with new or worsening BTKi-associated HTN.[10,15] Experts have recommended a variety of management strategies including referral to

cardiology or cardio-oncology when >2 anti-hypertensives are needed.[20] Using real-world, multicenter, retrospective data, we evaluated the antihypertensive effects of common medication classes and combinations in patients taking BTKis; although the vast majority of our patients were on ibrutinib and not one of the second-generation BTKis. During our evaluation, we distinguished between patients with HTN prior to ibrutinib initiation (prior-HTN), and those who developed incident HTN after starting ibrutinib (de novo HTN).

Methods

Study Population

We included randomly selected patients with lymphoid malignancies and a diagnosis of hypertension from 14 institutions in the United States. All patients were concurrently treated with a BTKi and anti-HTN therapy for at least 3 months between 2014 and 2018. They were then separated into two groups: those who were on anti-HTN mediations before starting a BTKi (prior-HTN) and those who started anti-HTN therapy after BTKi initiation (de novo HTN). Demographic variables such as lymphoid malignancy type and comorbidities were obtained, along with documentation of BTKi changes (dose reductions, medication discontinuation, and switching to an alternative BTKi). Anti-HTN medications were categorized into 4 major groups: ACEis and ARBs, BBs, calcium channel blockers (CCBs), and HCTZ. All timepoints for MAP measurements, medication start dates, and medication end dates were documented in relation to the index date, defined as the first date of concurrent BTKi and Anti-HTN agent use. Retrospective MAP data was assessed for each patient in relation to the type of anti-HTN drug or combination of drugs prescribed.

Institutional Review Boards at each site approved of the study prior to data acquisition. This was an investigator-initiated study funded by AstraZeneca. The study design, data collection and interpretation of data was conducted by all co-investigators. Data management and statistical analysis was done at the Fred Hutchinson Cancer Center which served as the coordinating site.

Outcomes

Our primary outcome was the clinical efficacy of different anti-HTN drug classes for the treatment of HTN in patients concurrently receiving a BTKi. Clinical efficacy, defined as effective anti-HTN treatment, was assessed by calculating mean MAP reductions in patients on various anti-HTN medications. We sought to identify if a single anti-HTN drug class or a combination of classes would reduce HTN in two patient groups: those with prior-HTN and those with de novo HTN.

Statistical analysis

Generalized estimating equations (GEE) were fit to assess the association of medication use with MAP, where each medication was classified into one of several broad categories. Indicators for each category were included in the GEE model based on presence of absence of the relevant medication at the time of MAP measurement. The impact of a specific two-drug combination was assessed by additionally including the following indicators in our regression model: an indicator for use of one of the two drugs alone, an indicator for use of the other drug in the combination alone, and an indicator for use of the two drugs at the same time. All two-drug combos were assessed; combinations of 3 or more were not feasible due to sample size restraints. Time from BTK inhibitor was included in the GEE models as a continuous linear variable, and race and sex were also included in the GEE models.

Summary lines on the figures were created using linear regression.

Results

Overall, 196 patients were included in the study: 118 received treatment for diagnosed HTN prior to starting a BTKi (prior-HTN) and 78 were diagnosed after BTKi initiation (de novo HTN). Of the prior-HTN patients, most had CLL/SLL (n=112, 94.9%) and were treated with ibrutinib (n=101, 85.6%). Of patients with de novo HTN; most had CLL/SLL (n=72, 92.3%) on ibrutinib (n=75, 96.2%). One patient (1.3%) in the de novo HTN group was on acalabrutinib, whereas 9 patients (7.6%) in the prior-HTN group were on acalabrutinib. In general, BTKi dose reductions and medication switches were uncommon across both groups; however, BTKis were permanently discontinued due to HTN in 26 (22.0%) of the prior-HTN patients and 18 (23.1%) of the de novo HTN patients. Additional baseline characteristics are described in Table 1.

Among patients with de novo HTN and prior-HTN, ACEis/ARBs constituted the most common anti-HTN drug class (66% of all patients) although CCBs (51%), BBs (36%) and HCTZ (29%) were also prescribed frequently (see Table 2). Common drug combinations included ACEi/ARBs with CCBs (27%), ACEi/ARBs with HCTZ (20%), CCBs with HCTZ (11%), and BBs with HCTZ (8%). The median number of MAP measurements per patient was 12 (interquartile range 7-19), and the median time from baseline to the end of follow-up was 3 years (interquartile range 1.4-4.8 years). For patients with de novo HTN, the median time from BTKi initiation to anti-HTN therapy initiation was 394 days (interquartile range 192-961 days).

MAP reductions with specific anti-HTN drug types and combinations

Of the patients with prior-HTN, no single anti-HTN class provided a statistically significant reduction in mean MAP, although all classes except CCBs showed non-significant reductions in mean MAPs (negative coefficients). In terms of two-drug combination therapies, only the combination of BBs and HCTZ provided a statistically significant mean reduction in MAP of -5.05 mmHg (95% CI -10.0 to -0.0596; p-value = 0.047; see Figure 1). The population that benefitted from this combination included patients who were on either a BB or HCTZ prior to starting a

BTKi and the second anti-HTN agent, as well as patients who were previously on an alternative anti-HTN regimen and began receiving both a BB and HCTZ after their BTKi start date.

Like prior-HTN patients, de novo HTN patients did not exhibit a statistically significant reduction in mean MAP after receiving any single anti-HTN class. De novo HTN patients also responded best to combination therapy, exhibiting a statistically significant mean MAP reduction on an ACEi/ARB combined with HCTZ (-5.47 mmHg; 95% CI -10.9 to -0.001; p-value = 0.05; see Figure 2). When all patients were combined, ACEi/ARBs plus HCTZ and BBs plus HCTZ provided statistically significant mean MAP reductions. Additional findings are outlined in Table 3.

MAP reductions seen with an increased number of concurrent anti-HTN drugs

As shown in Table 2, sixty-one percent of the patients were on more than one anti-HTN medication at any given time during follow-up. Across both pre-HTN and de novo HTN groups, 79 patients (40%) were on a maximum of 2 anti-HTN medications, 31 patients (16%) were on 3 anti-HTN medications, and 10 patients (5%) were on 4 or more agents concurrently. Patients in the de novo group exhibited a trend of MAP reduction with an increasing number of medications and a statistically significant mean MAP reduction (-5.70 mmHg) on 3 or more anti-HTN drugs (95% CI -9.94 to -1.46; p-value = 0.008) when compared to MAPs during periods of no anti-HTN drug use. Patients in the pre-HTN group had a suggestive mean MAP reduction on 4 or more anti-HTN drugs (reduction of -4.81 mmHg; 95% CI -9.93 to 0.30; p = 0.07) when compared with just one anti-HTN drug. When pre-HTN and de novo HTN groups were combined, a statistically significant mean reduction in blood pressure was seen in patients on 4 or more agents (reduction of -6.27 mm Hg; 95% CI -11.8 to -0.69; p = 0.02). Additional data pertaining to MAP reductions are available Table 4.

Percentage of Normotensive MAPs with specific anti-HTN drugs and combinations

Both anti-HTN combinations that provided statistically significant mean MAP reductions in all patients also led to the greatest percentage of normotensive MAPs, as defined by a systolic BP ≤120 and a diastolic BP ≤80. The definition of normotension was pulled from standard guidelines written for the American College of Cardiology/American Heart Association (ACC/AHA).[21] As shown in Figure 3, 17% of the MAPs collected for patients on an ACEi/ARB and HCTZ were in the normotensive range, the most of any single drug or combination of drugs used alone or with other agents. Second only to the combination of ACEis/ARBs with HCTZ, BBs plus HCTZ led to MAPS that were 13% normotensive.

Discussion

In this retrospective study evaluating the efficacy of different anti-HTN drug classes in patients with hypertension diagnosed prior to and after ibrutinib initiation, the greatest blood pressure reductions were seen in patients on combination therapies. Combination regimens with two or more drugs intuitively seemed to provide the best control, but two specific combination

regimens stood out once we controlled for the effects of all agents: beta blockers plus HCTZ provided a statistically significant mean MAP reduction in patients with prior-HTN, and ACEi/ARBs plus HCTZ provided a statistically significant mean MAP reduction in patients with de novo HTN. In all patients, these two combination regimens provided the greatest percentages of normotensive MAPs. Although prospective data will be needed to confirm whether these findings should inform formal guidelines on BTKi-related HTN; these data are hypothesis generating in identifying effective classes and combination regimens that appear to have real value in patients with BTKi-associated HTN.[10,15,20,22]

Multiple studies have shown a relationship between HTN and an increased risk of MACEs such as myocardial infarctions, stroke, heart failure, arrhythmias, and cardiac death, highlighting critical motivation for identifying optimal therapies to control HTN in the setting of BTKi use. Dickerson and colleagues used multivariate regression to show that new or worsened HTN was associated with an increased risk of MACEs (hazard ratio 2.17); however initiation of an anti-HTN medication mitigated this risk (hazard ratio 0.40).[14] More generally, a large body of literature unequivocally substantiates the claim that a person's life-time risk of developing cardiovascular disease is significantly higher if they have longstanding, severe HTN. In a study from the INTERHEART group, hypertension was responsible for 18% of the population-attributable risk of a first myocardial infarction.[23]

Nearly 90% of the patients in our study were treated with ibrutinib, in large part because the Food and Drug Administration (FDA) had not yet approved of acalabrutinib or zanubrutinib in patients with CLL prior to our data cut-off in 2018. Acalabrutinib received FDA approval for MCL in 2017 and CLL in 2019. Zanubrutinib received FDA approval for MCL in 2019 and CLL in 2023. Although second generation BTKis like zanubrutinib and acalabrutinib are considered more targeted and better tolerated than ibrutinib, data suggest patients taking second generation BTKis still face an increased risk of MACE. [24-26] Chen et al. found a 27% increase in the risk of MACE for each 5 mmHg increase in systolic BP (p-value <0.001) in patients on acalabrutinib.[11] Like our study, Chen et. al. also found that individual anti-HTN drug classes (include ACEis, ARBs, BBs, CCBs and diuretics) provided equivalent blood pressure control, whereas combination therapy with more than one drug class seemed to provide a superior -3.32 mmHg reduction in systolic BP.[11] We hope that future studies replicate our methods with second generation and noncovalent BTKis so as to identify the combination regimens that might provide the most benefit.

The 2017 multi-society hypertension guidelines do not have specific recommendations for patients on BTKis but do note that it would not be unusual for progressive hypertension to prompt the initiation or intensification of antihypertensive therapy in those on tyrosine kinase inhibitors such as sunitinib or sorafenib.[21] For the general population with hypertension, treatment with thiazide diuretics, an ACEi/ARB and/or CCB is recommended. Many patients will require ≥2 drugs from different pharmacologic classes to reach BP goals, which is consistent with our current study. Agents from different classes may even have a synergistic effect like the one between thiazides, which inadvertently stimulate the RAAS system, and ACEi/ARBs, which

counteract this compensatory mechanism. Perhaps this is why the combination of ACEi/ARBs with HCTZ was a particularly effective combination for patients with de novo HTN in our study. When patients require two or more medications to manage hypertension, consultation with a cardiologist should be considered for increased monitoring and to discuss the next best anti-HTN agent should the patient need three drugs.

The ESC 2022 cardio-oncology guidelines recognize the risk of arterial hypertension in patients treated with ibrutinib, along with other factors that may affect patients with lymphoid malignancies, such as stress, pain, steroid use, renal impairment, and reduced exercise.[27] Recommendations for antihypertensive therapy broadly encompass patients on any type of cancer treatment and suggest that an ACEi or ARB should be used as a first line treatment with the addition of a dihydropyridine CCB for those with a systolic BP ≥160 mmHg and diastolic BP ≥100mm Hg. Beta blockers may be especially effective in cancer patients with evidence of high sympathetic tone, stress, and/or pain.

Ultimately, larger prospective studies are needed to devise formal guidelines that aid clinicians in choosing optimal anti-HTN medications for patients on ibrutinib or second generation BTKis, especially since the median duration of ibrutinib treatment was 74 months during the 8-year follow-up from the RESONATE-2 study.[28] Given expectations for prolonged therapy, it would be useful to know if and when HTN resolves after a BTKi is reduced or discontinued in patients with de novo HTN. Our study may have contributed to current knowledge of BTKi-associated HTN by identifying specific combination therapies that may exhibit efficacy in this setting; but even here we noticed a relatively low percentage of normotensive MAPs in patients on the best drug combinations, proving there's room for improvement in all facets of our approach to BTKi-associated HTN.

We also acknowledge that comorbidities may drive the selection of certain anti-HTN agents when supportive data are convincing. For example, an ACEi/ARB and beta blocker are likely to be chosen in patients with a recent MI or a diagnosis of heart failure because these agents are known to reduce morbidity and mortality.[21,29] Some physicians may reach for ACEis/ARBs in all patients with chronic kidney disease because research shows a reduced risk of progression to end-stage kidney disease in patients with severely increased albuminuria.[30] An ACEi/ARB is also an appropriate first-line choice in a patient with diabetes mellitus (DM) and excessive albuminuria; whereas thiazide diuretics have an adverse effect on glucose metabolism.[31] Diuretics are typically avoided in patients susceptible to orthostatic hypotension, and beta blockers or calcium channel blockers tend to double as a rate control strategy in patients with atrial fibrillation.

Lastly, our showed that CCBs were not associated with a statistically significant MAP change either as monotherapy or when combined with other anti-HTN drugs. There is even a suggestion that CCBs may contribute to higher MAPs in patients on therapy to reduce BTKi-induced HTN. This phenomenon deserves further investigation, especially since CCBs are commonly used. Tang et al. has gone as far as suggesting that ACEis and ARBs might be

considered a first-line treatment option for BTKi-induced HTN, in part because they lack drug-drug interactions with BTKis.[32] However, caution is still warranted when using ACEis, especially since Munir et al. found that prior use of an ACEi was correlated with a risk of sudden or cardiac death in patients receiving ibrutinib and rituximab during the phase 3 FLAIR trial (RR 50.2; 95% CI 6.3 t 399; P<0.0001).[33]

Limitations

Our study had several limitations beyond the constraints of a small sample size, retrospective data and relatively few patients on second-generation BTKis. First, for the prior-HTN cohort, we did not evaluate the duration or severity of HTN prior to the index date. This means that we could not evaluate if starting a BTKi made a patient's known hypertension significantly worse. Furthermore, any possible worsening of a patient's hypertension seen immediately after BTKi initiation might have been the result of stopping or reducing an anti-HTN medication immediately prior to the index date, and not actually attributable to a BTKi.

Although this study evaluates hypertension management using a large-scale statistical model, it fails to provide details about decisions made between patients and providers to start specific anti-HTN medications or dose-reduce a BTKi. As such, we do not know how many patients started a BTKi at a reduced dose. We also do not know how often decisions to add or modify anti-HTN therapies hinged primarily on more aggressive treatment of cardiovascular risk factors or comorbidities like CKD.

Additionally, patients were only included if they had at least 3 months of real-world MAP data, but there were no stipulations on how many blood pressure measurements would be available during his period or any other interval. Large variations in blood pressure data are easily evident in both Figure 1 and Figure 2. Lastly, like the available data from clinical trials, all the BP measurements used in this study came from clinic visits. Given our expanding knowledge of real-world BP variations and the limitations of clinic measurements, we hope that wearable technologies and other reliable methods of acquiring real-world BP data may inform future studies on BTKi-induced HTN.

Conclusion

Treatment of HTN in patients taking ibrutinib is challenging, but combination therapies appear to be necessary in patients diagnosed with HTN before and after BTKi initiation. Patients with prior-HTN appear to benefit from combination regimens with BBs and HCTZ, whereas patients with de novo HTN appear to benefit from ACEi/ARBs with HCTZ. Large prospective studies are needed to formulate formal guidelines on the best anti-HTN regimens to use in patients taking a BTKi.

Authorship Contributions

Dr. Laura Samples completed this manuscript which was edited by all other listed authors. Dr. Mazyar Shadman led data collection and analysis efforts at the Fred Hutchinson Cancer Center. Jenna Voutsinas and Ted Gooley performed the statistical analysis for this project. All other authors not specifically listed were involved in study design, data collection, interpretation of data and reviewing and editing the manuscript.

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Conflict of Interest Disclosures

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Figure 1: MAP trend in patients with pre-existing HTN taking anti-HTN medications and a BTKi concurrently.

Figure 2: MAP trend in patients with de novo HTN taking anti-HTN medications and a BTKi concurrently.

Figure 3: Percentage of normotensive MAPs with specific BP medications/combinations in all patients.

Table 1: Patient Characteristics

		Prior-HTN (n=118)	De novo HTN (n=78)	Entire cohort (n=196)
Diagnosis	**CLL/SLL**	112 (94.9%)	72 (92.3%)	184 (93.9%)
	MCL	3 (2.5%)	3 (3.8%)	6 (3.1%)
	other	3 (2.5%)	3 (3.8%)	6 (3.1%)
BTKi type	**Ibrutinib**	101 (85.6%)	75 (96.2%)	176 (89.8%)
	Acalabrutinib	9 (7.6%)	1 (1.3%)	10 (5.1%)
	Other	8 (6.8%)	2 (2.6%)	10 (5.1%)
Current Treatment Line	**1**	57 (48.3%)	39 (50.0%)	96 (49.0%)
	2	32 (27.1%)	18 (23.1%)	50 (25.5%)
	3+	29 (24.6%)	21 (26.9%)	50 (25.5%)
Age; year median (range)		67.5 (42.0 - 88.0)	65.5 (37.0 - 87.0)	67 (37.0 - 88.0)
Race	**Caucasian**	100 (92.6%)	73 (97.3%)	173 (94.5%)
	Other	8 (7.4%)	2 (2.7%)	10 (5.5%)
	Missing	10	3	13
Sex	**Female**	34 (29.3%)	20 (25.6%)	54 (27.8%)
	Male	82 (70.7%)	58 (74.4%)	140 (72.2%)
History of DM		25 (21.2%)	9 (11.5%)	34 (17.3%)
History of CAD		5 (4.2%)	0 (0.0%)	5 (2.6%)
History of CKD		2	0	2
BTKi on a clinical trial		29 (24.6%)	17 (21.8%)	46 (23.5%)
BTKi dose reduction	**No**	84 (71.2%)	59 (75.6%)	143 (73.0%)
	Yes, for HTN	7 (5.9%)	2 (2.6%)	9 (4.6%)
	Yes, for other	27 (22.9%)	17 (21.8%)	44 (22.4%)
Time to BTKi dose reduction; Median days (range)		382.5 (0.0 - 1651.0)	365.0 (0.0 - 1574.0)	366.0 (0.0 - 1651.0)
Switch to other BTKi	**No**	111 (94.1%)	73 (93.6%)	184 (93.9%)
	Yes, for HTN	3 (2.5%)	2 (2.6%)	5 (2.6%)
	Yes, for other	4 (3.4%)	3 (3.8%)	7 (3.6%)
Time to switching to other BTKi; Median days (range)		308.0 (85.0 - 1631.0)	1445.0 (386.0 - 3775.0)	777.0 (85.0 - 3775.0)
BTKi stopped	**No**	92 (78.0%)	59 (75.6%)	151 (77.0%)
	Yes, for HTN	26 (22.0%)	18 (23.1%)	44 (22.4%)

	Yes, for other	0 (0.0%)	1 (1.3%)	1 (0.5%)

CAD: coronary artery disease; CKD: chronic kidney disease; DM: diabetes

Table 2: Frequency of BP medications/combination use among all patients

		Patients on the drug class	**Days on treatment (median)**
Anti-HTN class*	**ACEi/ARB**	66%	722
	CCB	51%	482
	Beta Blocker	36%	1036
	HCTZ	29%	690
BP drug combinations*	**ACEi/ARB + HCTZ**	20%	
	CCB + HCTZ	11%	
	Beta Blocker + HCTZ	8%	
	ACEi/ARB + CCB	27%	
Number of BP drugs prescribed at o time	**1**	39%	
	2	40%	
	3	16%	
	4+	5%	

ACEi: Angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blockers; CCB: Calcium channel Blockers;

*Indicates the percentage of patients taking this class or combination of alone or with other categories.

Table 3: Mean MAP reductions with specific BP medications/combinations

		95% Confidence interval		
	Estimate	Lower	Higher	p-value
Prior-HTN				
ACEi/ARB	-1.30	-4.74	2.13	0.45
Beta-Blockers	-2.06	-5.10	0.97	0.18
CCBs	2.33	-0.74	5.41	0.13
HCTZ	-1.17	-4.10	1.76	0.43
***Beta Blockers and HCTZ**	**-5.05**	**-10.0**	**-0.0596**	**0.047**
***de novo* HTN**				
ACEi/ARB	-0.13	-3.57	3.31	0.94
Beta-Blockers	-2.71	-6.88	1.45	0.20
CCBs	0.11	-5.66	5.90	0.96
HCTZ	-4.26	-9.46	0.93	0.10
***ACEi/ARB and HCTZ**	**-5.47**	**-10.9**	**-0.001**	**0.05**
All patients combined				
***ACEi/ARB and HCTZ**	**-3.16**	**-6.22**	**-0.10**	**0.04**
***Beta Blockers and HCTZ**	**-5.05**	**-9.61**	**-0.48**	**0.03**

MAP: Mean arterial pressure; ACEi: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin receptor blockers; CCBs: Calcium channel Blockers; HCTZ: Hydrochlorothiazide

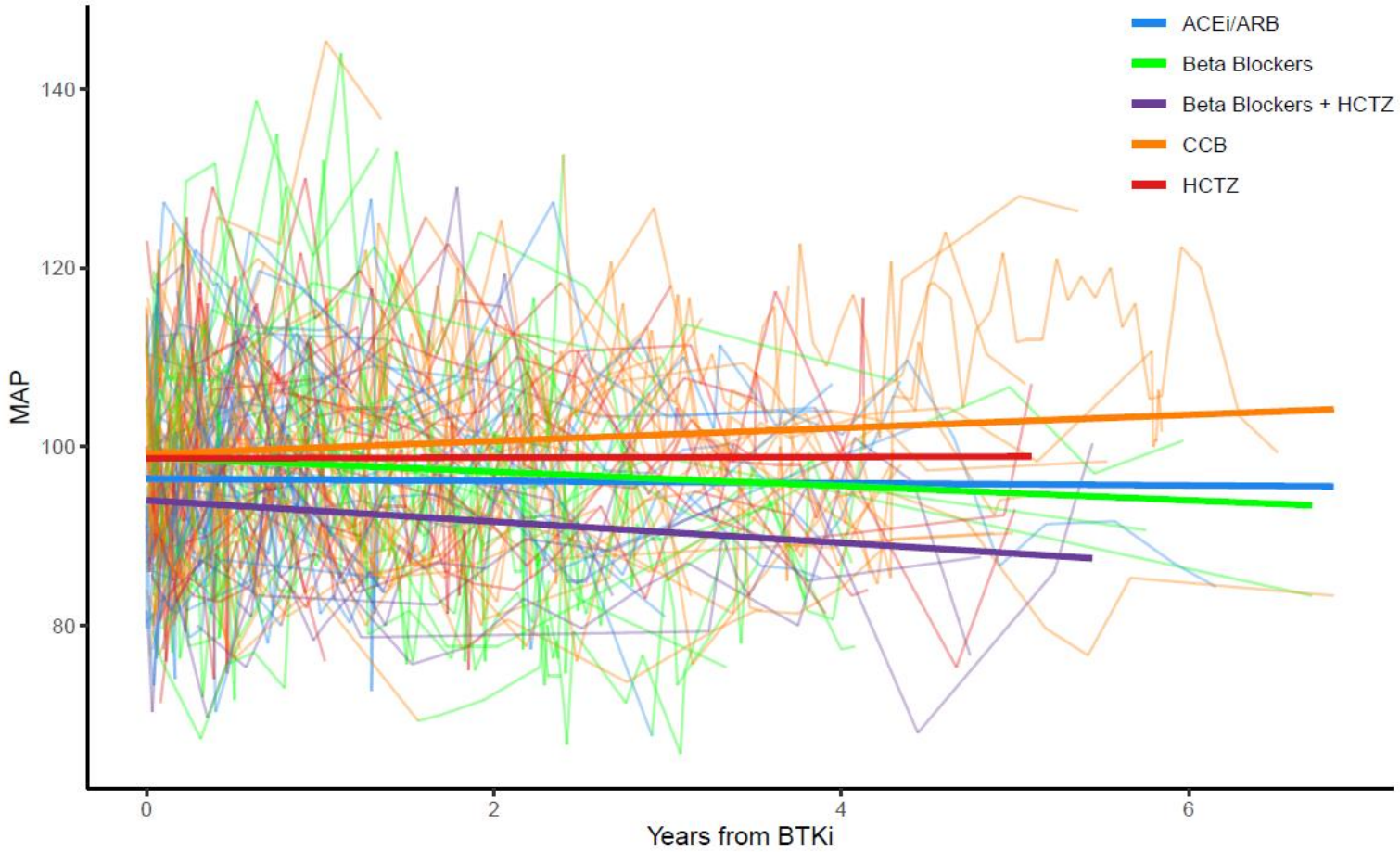
*Blood pressure combination was statistically significant after controlling for the possible of effects of a single drug class

Table 4: Mean MAP reduction per number of BP medications

		95% Confidence interval		
	Estimate	Lower	Higher	p-value
Prior HTN				
2 BP medications	-1.44	-4.72	1.84	0.39
3 BP medications	-0.23	-4.70	4.23	0.91
4+ BP medications	**-4.81**	**-9.93**	**0.30**	**0.07**
***de novo* HTN**				
1 BP medications	-2.08	-5.65	1.49	0.25
2 BP medications	-2.41	-6.43	1.61	0.24
3+ BP medications	**-5.70**	**-9.94**	**-1.46**	**0.008**
All patients combined				
1 BP medications	-1.06	-4.50	2.38	0.54
2 BP medications	-2.28	-5.93	1.36	0.22
3 BP medications	-1.60	-6.11	2.90	0.48
4+ BP medications	**-6.27**	**-11.8**	**-0.69**	**0.02**

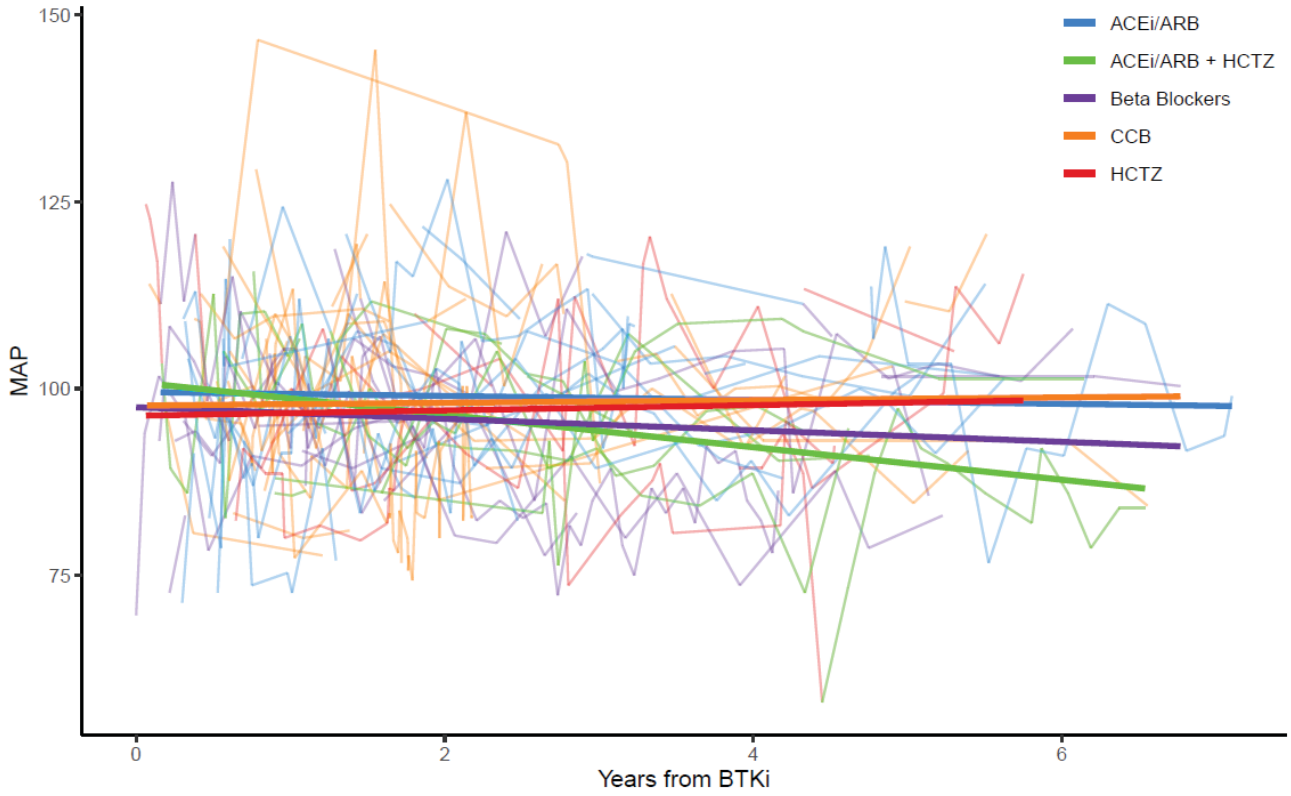
MAP: Mean arterial pressure; BP: Blood pressure

Figure 1: MAP trend in patients with pre-existing HTN taking anti-HTN medications and a BTKi concurrently.



ACEi/ARB: Angiotensin-converting-enzyme inhibitors/Angiotensin receptor blockers; BB: Beta blockers; CCB: Calcium channel blockers; HCTZ: Hydrochlorothiazide; MAP: Mean arterial pressure.

Figure 2: MAP trend in patients with de novo HTN taking anti-HTN medications and a BTKi concurrently.



ACEi/ARB: Angiotensin-converting-enzyme inhibitors/Angiotensin receptor blockers; BB: Beta blockers; CCB: Calcium channel blockers; HCTZ: Hydrochlorothiazide; MAP: Mean arterial pressure

Figure 3: Percentage of normotensive MAPs with specific BP medications/combinations in all patients.