

ABSTRACT

Employing a novel, comprehensive precision medicine clinical tool (PMCT) that is an LC/MS/MS-based platform (PrecisionCMQ™), we analyzed the serum of patients with hypertension (HTN) seeking emergency care ($n=295$) for the presence and quantity of 42 antihypertensive and cardiovascular medications. Patient-reported adherence was assessed by a validated 12-item survey; in exploratory analyses, a single item was used to classify patients as adherent/non-adherent. Adherence assessed by PMCT correlated with patient-reported adherence measured by the single-item survey. Among patients prescribed ≥ 3 antihypertensives, PMCT-based adherence was 77% in patients ($n=65$) who indicated they never miss a dose, versus 66% in patients ($n=71$) who reported missed doses ($p=0.02$, Kruskal-Wallis test; median prescribed medications = 3.6). Among patients with ≥ 3 prescribed antihypertensives, we found adherent patients had lower SBP (12.7 mm Hg lower, 95% CI 5.7-19.6; $p<0.01$) and DBP (7.5 mm Hg lower, 95% CI 3.1-11.9; $p<0.01$) after adjusting for age, sex, BMI, education, insurance status, administration of antihypertensives in ED and patient-reported adherence. No significant difference in BP was observed in patients prescribed 1 or 2 antihypertensives (*data not shown*). By comparing PMCT-based adherence to prescribed antihypertensives listed in the EHR, 11% of the detected medications (59/553) were not recorded in the patient's EHR. Additionally, to assess whether patients with higher serum medication concentrations had lower BP, we compared SBP and DBP to medication concentrations normalized to published reference ranges. After accounting for the above covariates and the number of detected medications, we observed a relationship between medication concentration and BP across patients. Adherence assessed by PMCT provided information beyond that available from patient-report alone. These results support the utility of clinical tool-based medication monitoring for assessing adherence and improving BP control in HTN patients.

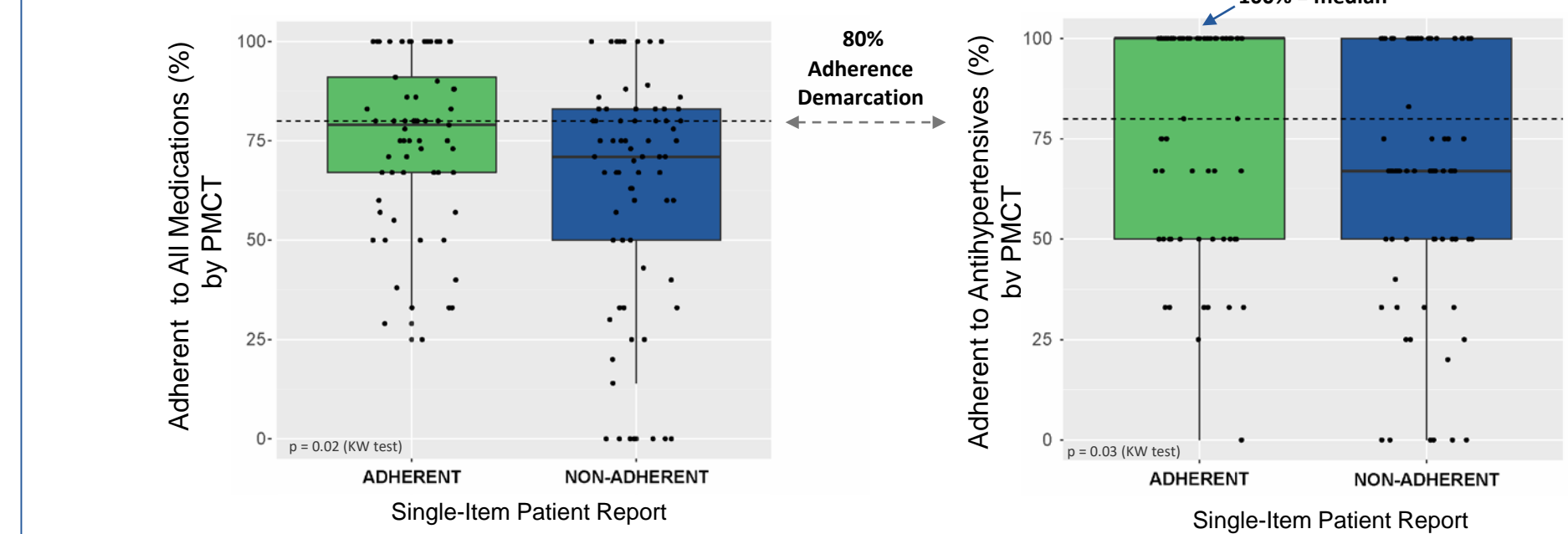
OVERVIEW

- We examined patient-reported adherence and PMCT-based adherence measures and compared these methods to blood pressure in patients reporting to ED with HTN
- PrecisionCMQ™ is a novel LC/MS/MS-based platform technology that facilitates the comprehensive measure of comorbid medications in the patient's *systemic circulation*
- Specifically, 42 antihypertensives were quantified to examine the correlation between lower blood pressure and *detected* medications in patient circulation
- PMCT medication monitoring can be used to assess adherence and improving BP control in HTN patients

STUDY PROCEDURES AND BIOANALYSIS

- Prospective, cross-sectional evaluation of patients with hypertension treated at Vanderbilt University Medical Center (VUMC), Adult emergency department 2012-2013
- Eligible patients (≥ 18 years) prescribed ≥ 1 of 14 common antihypertensives, had a VUMC primary care provider, and had not received their prescribed antihypertensive prior to enrollment
- Patients were excluded if they did not have a peripheral IV or declined venipuncture, were pregnant, unable to consent, or sought care for acute stroke or alcohol withdrawal, had previously enrolled, or had been in ED > 36 hours
- Research Assistants obtained consent & recorded demographic and clinical data; prescribed medications were determined by review of the medical record and patient interview
- Adherence assessed by PMCT was defined as $\geq 80\%$ of prescribed medications detected
- Patient-reported adherence was assessed by the Adherence to Refills and Medications Scale (ARMS; Kripalani et al. *Value in Health*, 2009, 12(1), 118-23). Non-adherent by the summed ARMS was defined as anything less than the maximum score of 48. For the single, 4-point Likert-like item, "How often do you forget to take your medicine", patients were classified as adherent ("None/Some") or non-adherent ("Most/All").
- Patients frozen serum samples sent to CAP Accredited Laboratory at Precera Bioscience, Inc.
- A novel LC/MS/MS test capable of quantitating 192 medications utilized in present study
- Sample analysis performed on Sciex QTRAP 5500 mass spectrometer/Analyst Software

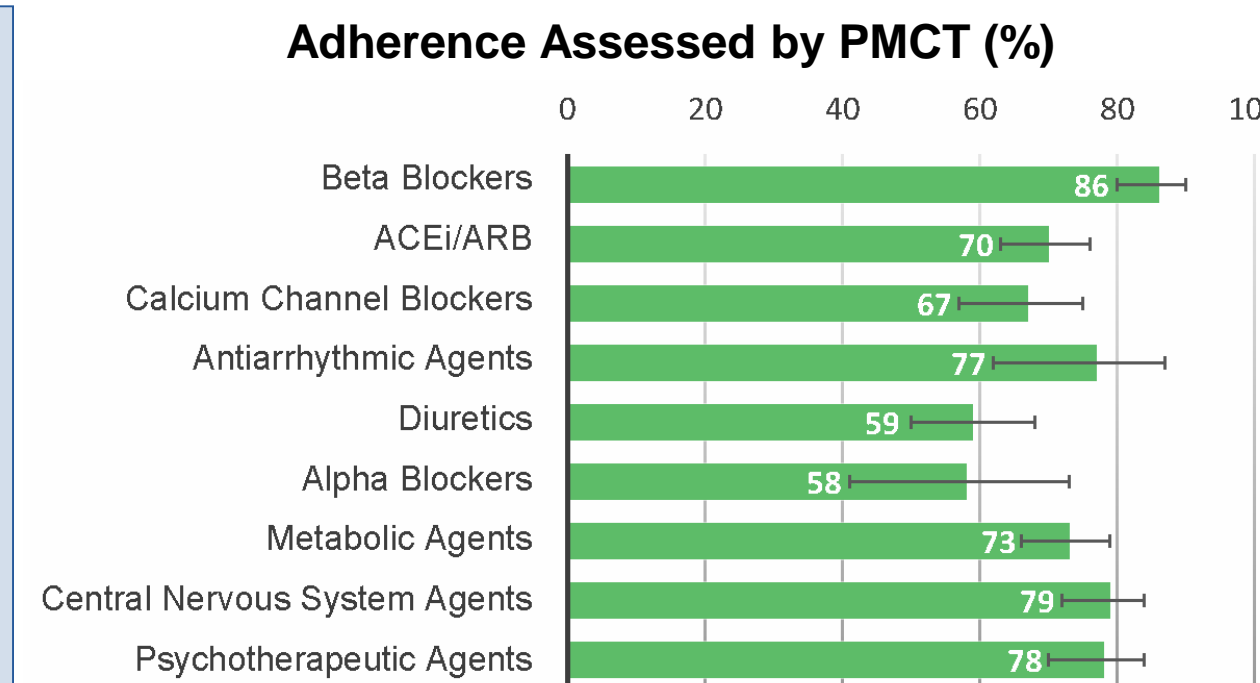
FIGURE 1. Adherent vs. Non-adherent by PMCT vs. Single-Item Patient Report: All Medications and Antihypertensive Medications



- The proportion of prescribed medications detected was calculated in patients prescribed ≥ 3 antihypertensives and compared to patient-reported adherence
- PMCT-based adherence to antihypertensives alone or all medications is significantly higher among patients who were adherent by single-item patient-report

Figure 2. Adherence to Medications by Class

- % Adherence obtained by pooling all medications within each class (95% CI, Wilson's method)
- Adherence was lower for diuretics and alpha blockers, higher for beta blockers



% Detections of Medications NOT in EHR

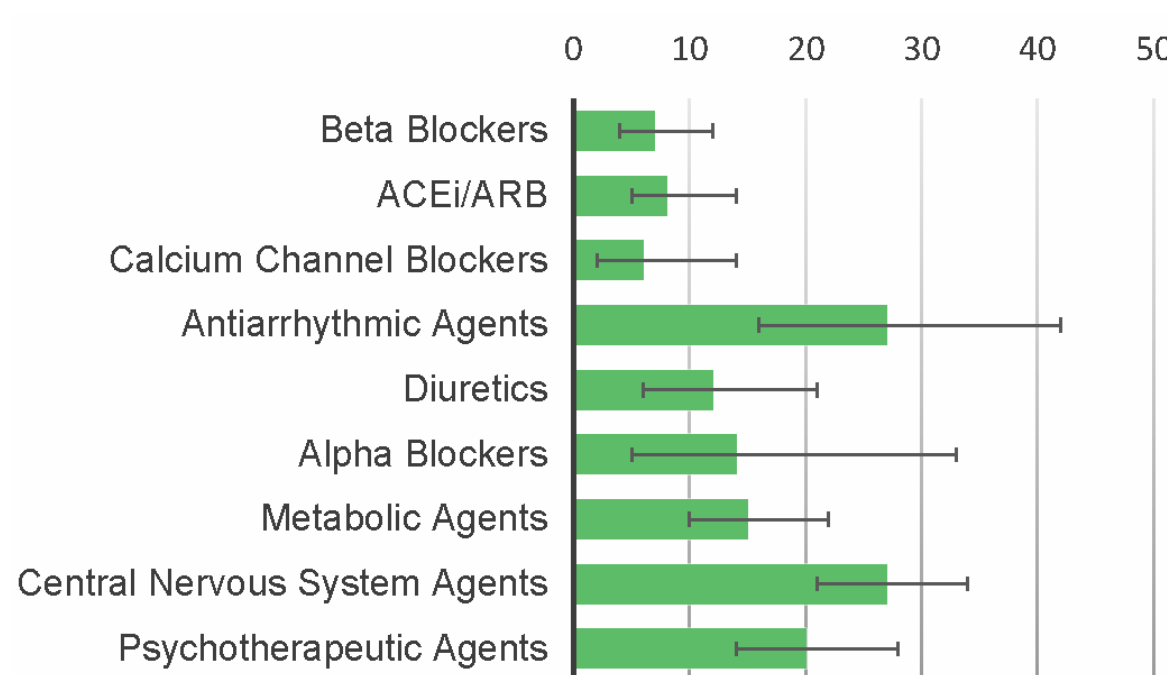
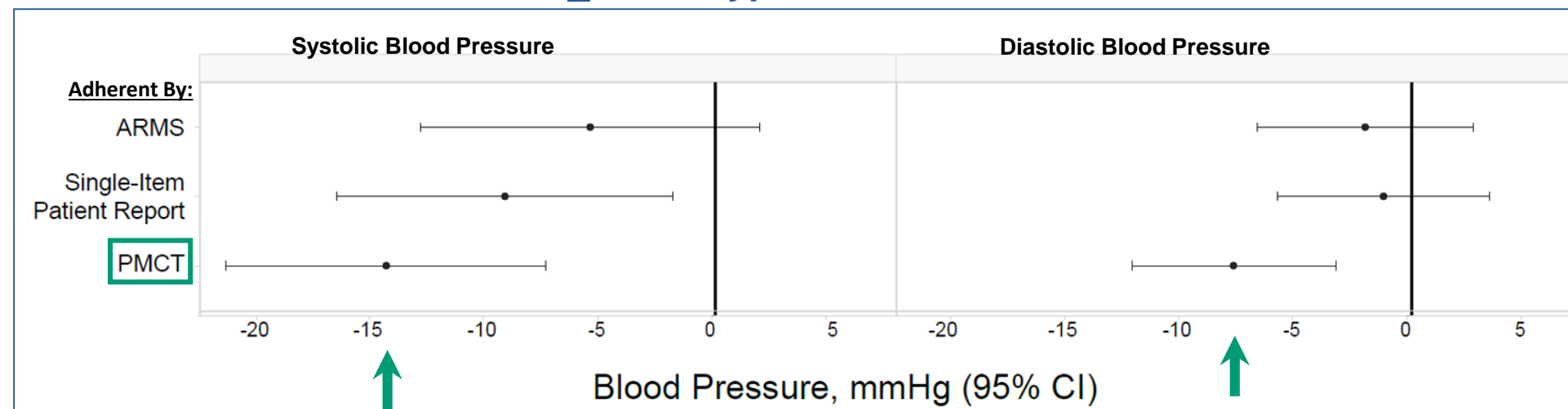


Figure 3. Detection of Medications Not Recorded in the Medication List (By Class)

- 59 of 553 medications detected (11%) were not recorded in the patient's medication list
- Antiarrhythmics administered in the ED are included

FIGURE 4. Adherence Assessed by PMCT and Patient-Self Reporting : Blood Pressure in Patients Prescribed ≥ 3 Antihypertensives



- Differences obtained after adjusting for several covariates using linear regression (age, sex, BMI, education, insurance status, administration of antihypertensives in ED; Cis and p-values by two-sided t-tests)
- Adherence was assessed by the PMCT, ARMS, and a single-item from the ARMS: "How often do you take your meds?"
- Among patients prescribed ≥ 3 antihypertensives, mean SBP/DBP were lower for adherent vs. non-adherent patients when assessed by PMCT (SBP, 12.7 mm Hg lower; 95% CI 5.7-19.6; DBP, 7.5 mm Hg lower; 95% CI 3.1-11.9)
- Adherence assessed by PMCT added important information beyond the single-item patient-report in predicting SBP ($p<0.01$) and DBP ($p<0.01$)

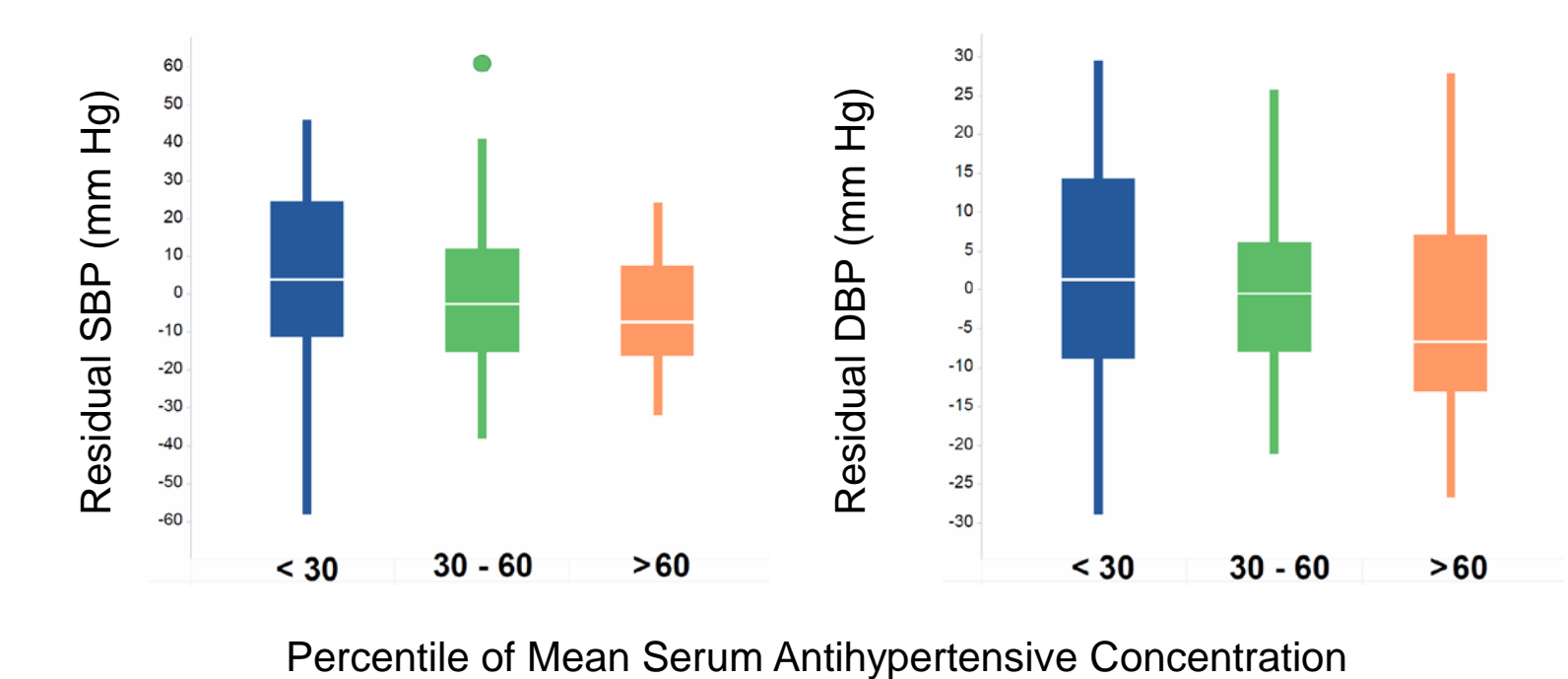
Clinical study portion (CDM, VUMC) of this investigation funded in part by CTSA award No. UL1TR000445 & VR3269, and K12HL109019 & K23HL125670

Table 1. Comprehensive Detection of Medications by Class in Hypertensive Patients

	Medication	Rx	Detected	% Adherence (95% CI)
ACEi & ARB	lisinopril	42	30	70 (61, 77)
	losartan	10	8.1	67 (49, 81)
	valsartan	4.4	3.4	69 (42, 87)
	ramipril	2.7	2.4	75 (41, 93)
	enalapril	1	1.4	100 (44, 100)
	telmisartan	1	1.4	100 (44, 100)
	irbesartan	1	1	67 (21, 94)
	quinapril	1	1	100 (44, 100)
	benazepril	1	0.7	67 (21, 94)
	olmesartan	0	0.3	
Alpha Adrenergic	tamsulosin	6.1	4.4	75 (51, 90)
	clonidine	5.1	1.7	38 (18, 64)
	terazosin	0.7	0.7	100 (34, 100)
Antiarhythmics	doxazosin	0.7	0	0 (0, 66)
	guanfacine	0	0.7	
	diltiazem	7.1	8.1	100 (85, 100)
	verapamil	2.7	2.4	88 (53, 98)
	amiodarone	2.4	0	0 (0, 35)
	quinidine	0	1.4	
	dofetilide	0	1	
	dronedarone	0.7	0.3	50 (9, 91)
	flecainide	0.3	0.3	100 (21, 100)
	procainamide	0	0.3	
Beta Adrenergic	metoprolol	34	32	88 (80, 93)
	carvedilol	15	13	81 (67, 90)
	atenolol	6.1	6.4	100 (82, 100)
	labetalol	1.4	1	75 (30, 95)
	propranolol	1.4	1	75 (30, 95)
	nebivolol	0.7	0	0 (0, 66)
Ca Channel	nadolol	0.3	0.3	100 (21, 100)
	amlodipine	22	16	65 (53, 76)
	nifedipine	11	8.1	73 (56, 85)
	felodipine	0.3	0	0 (0, 79)
	HCTZ	31	18	54 (44, 64)
	furosemide	23	11	42 (30, 54)
Diuretics	torsemide	2.7	3	100 (68, 100)
	triamterene	3	2.4	78 (45, 94)
	bumetanide	1.4	1.4	50 (15, 85)
	metolazone	1.4	1	33 (6, 79)
	chlorthalidone	0.7	1.4	100 (34, 100)
	chlorothiazide	0	1	
acetazolamide	0.3	0	0 (0, 79)	

- Prescriptions (Rx) expressed per 100 patients
- Detections of medications expressed per 100 patients
- Confidence intervals calculated using Wilson's method

FIGURE 5. Blood Pressure by Tertiles of Antihypertensive Serum Concentration



- Medication concentration is expressed as a percentile of medication(s) concentration from *all currently available clinical samples* (i.e., *Precera Data Base*); percentile values were averaged across antihypertensive medications
- Residual blood pressure was determined by a multiple linear regression model that included age, sex, BMI, education, insurance status, administration of antihypertensives in ED, and PMCT among patients prescribed ≥ 3 antihypertensives ($N = 136$)
- PMCT quantitation results were associated with BP, demonstrating that medication concentration (*and not simply detections*) are associated with blood pressure in patients with hypertension prescribed ≥ 3 antihypertensives

SUMMARY

- Precision Medicine Clinical Tool-based (PMCT) adherence to medications was 77% in patients who reported they never miss a dose of their medication
- Adherence assessments by PMCT add important information beyond patient-reported adherence in predicting systolic and diastolic blood pressure
- Medication concentration determined by PMCT (and not simply adherence) are associated with blood pressure in patients with hypertension prescribed ≥ 3 antihypertensives