Original Article

Nonadherence to antihypertensive medications is related to pill burden in apparent treatment-resistant hypertensive individuals

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Objective: Nonadherence to medication is present in at least 50% of patients with apparent treatment-resistant hypertension. We examined the factors associated with nonadherence as detected by a liquid chromatography-tandem mass spectrometry (LC-MS/MS)-based urine antihypertensive drug assay.

Methods: All urine antihypertensive test results, carried out for uncontrolled hypertension (BP persistently >140/90 mmHg) between January 2015 and December 2016 at a single toxicology laboratory were analysed. Drugs detected were compared with the antihypertensive drugs prescribed. Patients were classified as adherent (all drugs detected), partially nonadherent (at least one prescribed drug detected) or completely nonadherent (no drugs detected). Demographic and clinical parameters were compared between the adherent and nonadherent groups. Binary logistic regression analysis was performed to determine association between nonadherence and demographic and clinical factors.

Results: Data on 300 patients from nine hypertension centres across the United Kingdom were analysed. The median age was 59 years, 47% women, 71% Caucasian, median clinic BP was 176/95 mmHg and the median number of antihypertensive drugs prescribed was four. One hundred and sixty-six (55%) were nonadherent to prescribed medication with 20% of these being completely nonadherent. Nonadherence to antihypertensive medication was independently associated with younger age, female sex, number of antihypertensive drugs prescribed, total number of all medications prescribed (total pill burden) and prescription of a calcium channel blocker.

Conclusion: This LC-MS/MS urine analysis-based study suggests the majority of patients with apparent treatment-resistant hypertension are nonadherent to prescribed treatment. Factors that are associated with nonadherence, particularly pill burden, should be taken into account while treating these patients.

Keywords: adherence, antihypertensive, hypertension, liquid chromatography-tandem mass spectrometry, resistant, screening

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BHF, British Heart Foundation; BP, blood pressure; eGFR, estimated glomerular filtration rate; ESC-ESH, European Society of Cardiology – European Hypertension Society; IBM, International Business Machines; LC-MS/MS, liquid chromatography-tandem mass spectrometry; NHS, National Health Service (in the UK); OR, odds ratio; ROC, receiver operating characteristic; SPSS, Statistical Package for the Social Sciences; TRH, treatment-resistant hypertension

INTRODUCTION

Hypertension is one of the most important preventable causes of premature morbidity and mortality throughout the world. In 2017, globally, 10.4 million deaths and 218 million disability-adjusted life-years were attributable to high SBP [2]. Treatment-resistant hypertension (TRH) is reportedly present in 5–30% of the total hypertensive population [1–6]. It is defined as office BP above 140/90 mmHg whilst on at least three antihypertensive agents (one of which is usually a diuretic) at optimal or maximum tolerated doses [7–10].

Patients with TRH are nearly 50% more likely to develop a cardiovascular event compared with those without [11]. One study estimated the risk of developing a fatal or

nonfatal cardiovascular event over 5 years to be 2.4-fold higher in TRH compared with non-TRH [12]. Another analysis of 470 386 hypertensive patients from a single healthcare system showed that patients with TRH, compared with non-TRH, had increased risks of end-stage kidney disease, ischaemic heart disease, heart failure, stroke, and mortality; with multivariable adjusted hazard ratios (95% confidence intervals) of 1.32 (1.27–1.37), 1.24 (1.20–1.28), 1.46 (1.40–1.52), 1.14 (1.10–1.19), and 1.06 (1.03–1.08), respectively [13]. A post hoc analysis of Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) suggests that the risks of end-stage kidney disease, cardiovascular events and mortality may be even higher than that found in the aforementioned study [14].

However, the true prevalence of TRH is difficult to determine because of apparent resistance because of white-coat hypertension, poor adherence with prescribed medication, poor BP measurement techniques and inappropriate combination of treatment [15,16]. Notwithstanding the poor prognosis, as many as 53% of those with TRH are reported to be nonadherent to their prescribed medication [17]. Until recently, however, no simple, objective test of adherence existed, with commonly used indirect methods, such as patient interview, prescription refill, and pill counts often inaccurate. Supervised administration of medications and monitoring of BP in directly observed therapy clinics are more accurate but costly in regards to bed/clinic usage and staff time, inconvenient and sometimes harmful to nonadherent patients [15,16].

This need, coupled with the increased availability of more sensitive and robust mass spectrometry instrumentation, has led our group and others [17–19] to develop an objective test of adherence that is easy to administer, quick, inexpensive, and reliable, in order to identify patients with true resistance to antihypertensive drugs to optimize their treatment.

The aims of this retrospective analysis were: to determine the prevalence of nonadherence in a cohort of apparent TRH using a well validated, liquid chromatography-tandem mass spectrometry (LC-MS/MS)-based urine drug assay [16]; and to ascertain the risk factors for nonadherence using routinely collected demographic and clinical parameters.

MATERIALS AND METHODS

Study population

All patients with uncontrolled hypertension (clinic BP >140/90 mmHg on treatment) presenting to nine hypertension centres across the United Kingdom who had urine antihypertensive assay carried out in a single toxicology laboratory between January 2015 and December 2016. The centres included were Heartlands Hospital, Birmingham; University Hospitals Coventry and Warwickshire NHS Trust, Coventry; University Hospitals Bristol NHS Foundation Trust, Bristol; Barts Heart Centre, London; Queen Elizabeth Hospital, Birmingham; University Hospitals of North Midlands NHS Trust, Stoke on Trent; Royal Wolverhampton NHS Trust, Wolverhampton; and the BHF Centre of Research Excellence, Edinburgh. All patients provided verbal consent for urine drug testing but they had not been informed beforehand that drug testing would be carried out at their clinic visit.

Clinical assessment

All patients had white-coat hypertension excluded by ambulatory BP monitoring (by home BP in a few patients who did not tolerate or refused ambulatory monitoring), and secondary hypertension by appropriate investigations as per hospital protocol in each centre. Demographic details, clinic BP (taken using a validated BP monitor), estimated glomerular filtration rate (eGFR), body weight, BMI, and list of all medications including antihypertensive medication were collected at clinic visits and recorded on urine analysis request forms for all patients. These data were used for analyses in this study.

Drug analysis

All urine samples received for urinary antihypertensive drug screening during the timeframe were analysed using the method outlined elsewhere [19]. Briefly, standards or samples (50 μl) were manually pipetted into a 1.1 ml screw-topped conical glass vial. To this, 150 μl of an internal standard solution containing deuterated amlodipine, bisoprolol, doxazosin, hydrochlorothiazide and ramipril was added. Samples were vortex mixed for 10 s and transferred to the LC-MS/MS instrument for analysis. For the period of audit, the LC-MS/MS assay detected the following drugs and metabolites: amlodipine, felodipine nifedipine, verapamil, diltiazem, lisinopril, perindopril, ramipril, enalapril, losartan, irbesartan, candesartan, indapamide, furosemide, bendroflumethiazide, hydrochlorothiazide, spironolactone metabolite, atenolol, labetalol, bisoprolol, metoprolol, doxazosin and moxonidine.

Data analysis

All urine antihypertensive test results performed for apparent TRH patients between January 2015 and December 2016 at Heartlands Hospital toxicology laboratory were included in the data set. Drugs detected were compared with the antihypertensive drugs prescribed. Patients were classified as adherent (all drugs detected) or nonadherent (at least one prescribed drug not detected). None of the individuals in the present cohort was on a drug that was not detectable by the assay.

Statistical Package for the Social Sciences (SPSS) version 22 (IBM) was used for statistical analysis. Demographic and clinical data were compared across the two groups using a Mann–Whitney U, for the continuous variables, which were nonparametric). Pearson chi-square test was used for categorical variables. The parameters compared were age, sex, ethnicity, body weight, BMI, eGFR, clinic SBP and DBP readings at the point of urine testing, total number of medications prescribed (total pill burden) and number of antihypertensive medications prescribed. Class of drugs prescribed [angiotensin-converting enzyme inhibitors (ACE-I), angiotensin II receptor antagonists (ARB), beta-blockers, calcium channel antagonists, diuretics and other antihypertensive medications] were also compared with adherence class.

Binary logistic regression was used to generate prediction models for overall nonadherence [20]. Adherence status was used as the binary-dependent variable, where nonadherence was defined as absence of at least one antihypertensive in the urine antihypertensive assay. A preliminary analysis was carried out, which included all basic demographics (age, sex, ethnicity) and clinically relevant variables (SBP and DBP, eGFR, BMI, total pill burden, number of prescribed antihypertensive drugs and antihypertensive drug classes). Variables that were significantly different ($P < 0.05$) between the adherent and nonadherent groups were included in the regression model. Thus, the final prediction model was adjusted for sex, age, SBP and DBP, eGFR, number of prescribed antihypertensive drugs, total pill burden, and a binary variable indicating whether a patient was prescribed calcium channel blockers and diuretics (model 1). To check for the sensitivity of the missing values, a second model was produced, which was adjusted for sex, age, number of antihypertensives, calcium channel blocker and diuretic use (model 2). The models' generalizability was evaluated using receiver-operating characteristic (ROC) curve to estimate the area under the curve. Nagelkerke pseudo R^2 was used to summarize the proportion of variation in the dependant variable associated with the predictor or independent variables.

As this analysis was conducted as part of a clinical audit project, Research Ethics Committee approval for the study was not required.

RESULTS

Three hundred and twenty-two urine samples from nine hypertension centres across the United Kinddom were received for analysis during the timeframe. Nineteen patients were excluded for duplicate urine samples received and three for missing gender description. Thus, 300 patients were included in the analysis: the median age was 59 years, 47% were women and 71% Caucasian. The demographic and clinical characteristics of the patients are shown in Table 1.

The median number of antihypertensive drugs prescribed was four; 166 (55.3%) were nonadherent to
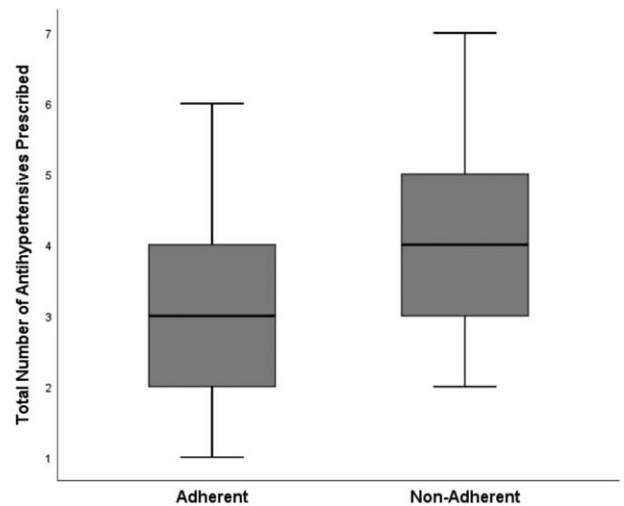
FIGURE 1 Number of antihypertensive drugs prescribed in relation to adherence status ($n = 300$). Box-and-whisker plot to illustrate differences in antihypertensive medications prescribed (median and IQR, $P < 0.001$).

prescribed medication with no prescribed drug detected in 60 (20%) of patients. Nonadherent patients were younger with a median age of 57 years compared with 66 years in the adherent group ($P < 0.001$). There were more women (54 vs. 37%, $P < 0.001$) (Fig. 1). Nonadherent patients had higher SBP (mean 181 vs. 172 mmHg, $P = 0.027$) and DBP (100 vs. 90 mmHg, $P < 0.001$); and they were on higher number of antihypertensive drugs (median 4 vs. 3, $P < 0.001$, Table 1 and Fig. 1) and total number of drugs prescribed (median 7 vs. 5, $P < 0.001$, Table 1 and Fig. 2). They also had higher median eGFR (76 ml/min per 1.73 m^2) compared with adherent patients (66 ml/min per 1.73 m^2). More patients in the nonadherent group were prescribed calcium channel blockers (87 vs. 59%) and diuretics (84 vs. 64%) compared with the adherent group (Table 2). Figure 3 shows the number of drugs in each class of antihypertensive agents prescribed vs. number detected on urine testing. Further sensitivity analysis suggested that dihydropyridine calcium channel blockers were more likely to be associated with nonadherence (66.3% in nonadherent group, 33.7% in adherent group, $P < 0.0001$) than the nondihydropyridine

TABLE 1. Demography and clinical parameters

	Percent missing data	All patients	Adherent	Nonadherent	*P*
Number of patients (%)	0	300	134 (44.7)	166 (55.3)	–
Female (%)	0	141 (46.8)	52 (36.9)	89 (63.1)	0.004
Age (years)	0	59 (49–70)	66 (55–74)	57 (48 - 64)	<0.001
Non-Caucasian (%)	26	65 (29.3)	28 (43.1)	37 (56.9)	0.721
Antihypertensive drugs prescribed	0	4 (3–5)	3 (2–4)	4 (3–5)	<0.001
CCB	0	223 (74.3)	79 (59.0)	144 (86.7)	<0.001
RASi	0	255 (85.0)	108 (80.6)	147 (88.6)	0.055
Diuretic	0	226 (75.3)	86 (64.2)	140 (84.3)	<0.001
Beta blocker	0	136 (45.3)	57 (42.5)	79 (47.6)	0.382
Other	0	184 (61.3)	74 (55.2)	110 (66.3)	0.051
Total drugs prescribed	24.4	6 (4–8)	5 (4–7)	7 (5–10)	<0.001
SBP (mmHg)	22.7	176 (160–197)	172 (158–188)	181 (161–201)	0.025
DBP (mmHg)	22.7	95 (81–110)	90 (75–105)	100 (84–115)	<0.001
eGFR (ml/min per 1.73 m^2)	20	71 (55–86)	66 (51–79)	76 (61–89)	0.001
BMI (kg/m^2)	41	31.4 (28.4–35.5)	31.0 (28.8–36.0)	31.6 (27.8–34.9)	0.436

All continuous variables reported as median (IQR). All count variables presented as n (%). BP, blood pressure (clinic); CCB, calcium channel blocker; eGFR, estimated glomerular filtration rate; RASi, renin–angiotensin system inhibitor.
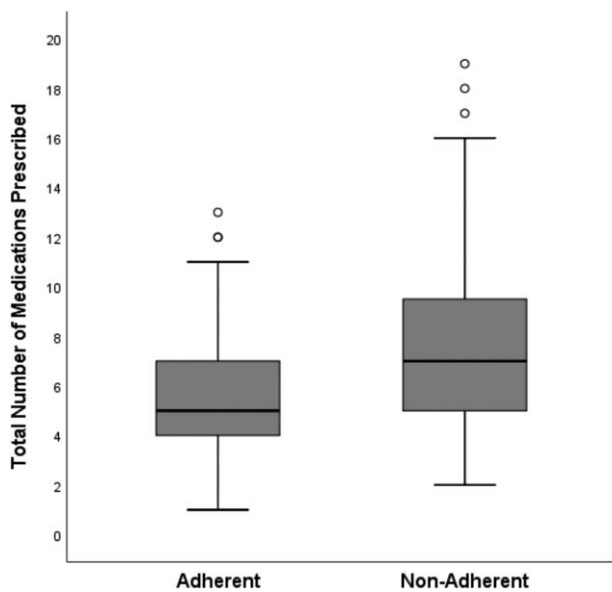
FIGURE 2 Number of all drugs prescribed in relation to adherence status ($n = 227$). Box-and-whisker plot to illustrate differences in all drugs prescribed (median and IQR, $P < 0.001$).

calcium channel blocker (55.6% in nonadherent group, 44.4% adherent group, $P = 1$).

We also conducted an exploratory comparative analysis of demographic and clinical correlates of complete nonadherence and partial nonadherence. Those who were completely nonadherent were younger (median age 53 vs. 58 years, $P = 0.033$) and there were more men (54 vs. 46%, $P = 0.003$) in the complete nonadherence group. All of the other parameters were equally distributed between the groups.

A logistic regression was performed on 206 patients with complete data on all variables, to ascertain the effects of sex, age, SBP and DBP, number of all prescribed antihypertensive medications, prescribed diuretics and calcium channel blockers, and total number of all medications prescribed on the odds that patients are nonadherent to antihypertensive medications (Table 2). The logistic regression model was statistically significant, χ^2 (df 4) $= 80.8$, $P < 0.001$, Nagelkerke $R^2 = 43.3\%$, correctly predicted 73.3% and the area under the curve for this logistic regression model was 0.79 [confidence interval (CI) 0.74–0.84; $P < 0.001$] suggesting a fair level of discrimination.

In this model (model 1, $n = 206$) female sex, total pill burden, higher number of antihypertensive drugs and prescription of calcium channel blockers were all associated with a higher odds ratio (OR) of nonadherence; whilst increasing age was associated with lower OR of nonadherence. Model 2 ($n = 298$, after excluding variables with missing data), supported the results (Table 2). Figure 4 shows the probability of nonadherence in each age quartile in relation to sex, the number of antihypertensive drugs prescribed and prescription of calcium channel blockers.

DISCUSSION

This study, using a LC-MS/MS-based urine drug assay in 300 patients with apparent TRH from nine hypertension centres in the United Kingdom, demonstrated that 55% of patients were nonadherent to their prescribed medications with 20% being completely nonadherent. Younger age, female sex, total pill burden, number of antihypertensive drugs prescribed and prescription of calcium channel blockers were independently associated with nonadherence.

Suboptimal adherence or nonadherence is common in all chronic conditions; on average around 50% of all prescribed medications for chronic conditions are not taken as prescribed [21,22]. The conditions most frequently studied have been HIV/AIDS, tuberculosis, epilepsy, psychiatric disorders, asthma, chronic obstructive pulmonary disease, cardiovascular disease or cardiovascular risk, hypertension and diabetes [21,23]. Medication wastage because of nonadherence places an enormous cost burden on the healthcare system [24].
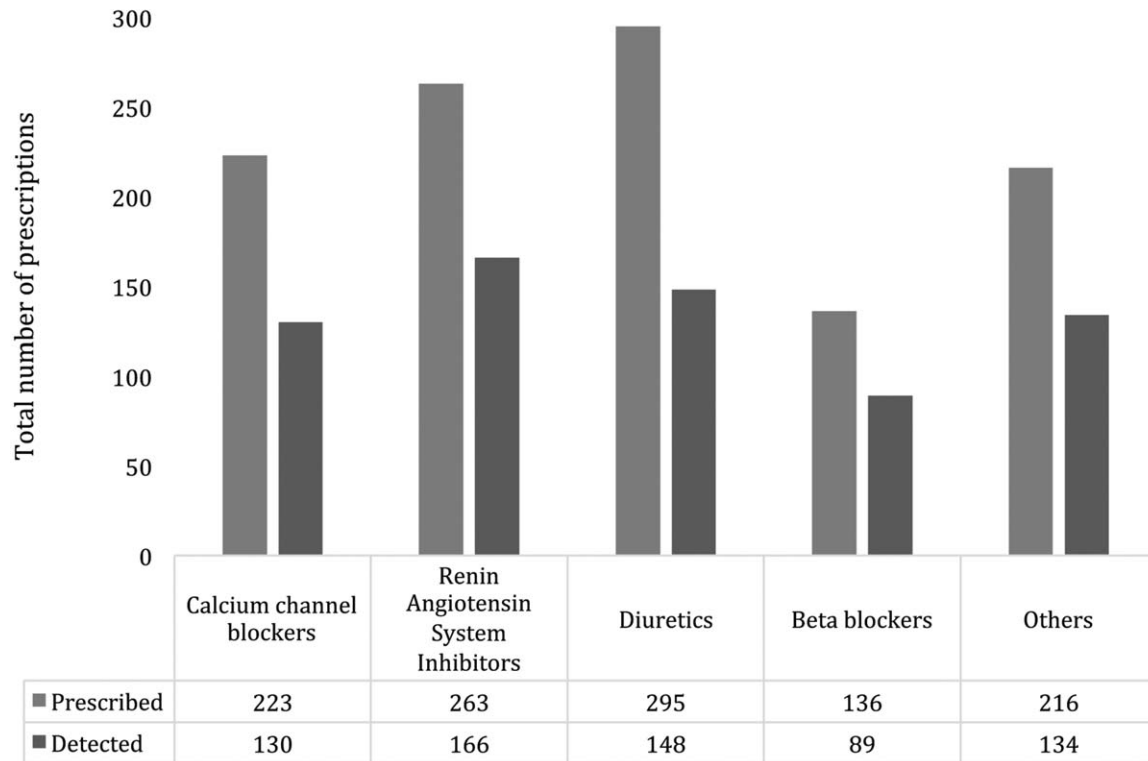
In hypertension, the reported prevalence rate of nonadherence varies between 3 and 65% [15–18,25,26]. This wide variation may be related to the method of assessment and the study population. Studies that used a direct method of assessment – for example, drug screening using LC-MS/MS or directly observed therapy – report a higher prevalence of nonadherence compared with those that used an indirect method, such as prescription refill rate or patient interview. Similarly, studies involving patients with apparent TRH report a much higher prevalence of nonadherence compared with studies in unselected cohorts of hypertensive individuals. The prevalence rate of 55% in our study is similar to other studies that used urine drug monitoring in cohorts of apparent TRH [17,25].

TABLE 2. Factors associated with nonadherence to antihypertensive medications

Variables	Model 1 ($n = 206$)			Model 2 ($n = 300$)		
	Odds ratio	95% CI	P	Odds ratio	95% CI	P
Age	0.97	0.94–1.00	0.082	0.96	0.94–0.98	<0.001
Female sex	3.18	1.53–6.59	0.002	2.76	1.58–4.82	<0.001
Number of antihypertensives prescribed	1.69	1.11–2.58	0.015	1.74	1.32–2.29	<0.001
CCB	3.51	1.51–8.16	0.004	2.66	1.37–5.19	0.004
Diuretic	0.79	0.30–2.09	0.643	1.56	0.75–3.27	0.234
Total medication	1.18	1.01–1.37	0.032			
SBP	1.00	0.99–1.02	0.761			
DBP	1.02	1.00–1.05	0.048			
eGFR	1.013	0.99–1.03	0.112			

Binary logistic regression analysis of factors associated with nonadherence to antihypertensive medications adjusted for age, sex, clinic SBP and clinic DBP, estimated glomerular filtration rate (eGFR), number of antihypertensive drugs prescribed, prescriptions of calcium channel blocker (CCB) and diuretic, and total number of medications (antihypertensive and other medications) prescribed. CI, confidence interval.

Number of antihypertensives prescribed and detected according to class

	Calcium channel blockers	Renin Angiotensin System Inhibitors	Diuretics	Beta blockers	Others
■ Prescribed	223	263	295	136	216
■ Detected	130	166	148	89	134

FIGURE 3 Graphical illustration of the number of medications in each antihypertensive class prescribed and detected in urine. Calcium channel blockers: Amlodipine, Nifedipine, Felodipine, Diltiazem, Verapamil. Renin–angiotensin system inhibitors: Lisinopril, Perindopril, Ramipril, Losartan, Irbesartan, Candesartan, Enalapril. Diuretics: Indapamide, Bendroflumethiazide, Hydrochlorothiazide, Furosemide, Spironolactone. Beta blockers: Atenolol, Bisoprolol, Labetalol, Metoprolol. Others: Doxazosin, Moxonidine.

The patient cohort in this study was derived from nine hypertension clinics across the United Kingdom. The median number of antihypertensive agents prescribed was four, and all of the patients had secondary hypertension and white-coat effect excluded before urine drug screening was carried out. Therefore, this was a group of patients with apparent resistance to antihypertensive treatment. Observational cohort or cross-sectional studies from specialist hypertension centres form the mainstay of studies describing the prevalence of nonadherence among patients with TRH reporting high nonadherence rate (50–65%) using serum or urine drug assays [17,25,26]. On the other hand, population studies using indirect measures of adherence in large populations report much lower nonadherence rates [27,28].

A recent systematic review summarized 24 published studies reporting adherence in TRH [25]. There was an average of 86 patients from 21 studies, the largest of which included 339 patients. Pooled mean nonadherence rate was 31.2%, with the highest rates reported in studies that used direct methods testing patients' sera or urine, followed by studies that used directly observed therapy (47.9 and 44.6%, respectively). The lowest rate of nonadherence was found in a study reporting on medication possession ratio at 3.3%.

There were significant differences in demographic and clinical parameters between adherent and nonadherent patients in this study. Younger age, female sex, number of antihypertensive medications prescribed and the prescription of calcium channel blockers were independently associated with antihypertensive drug nonadherence. These findings are consistent with a recently published study of 1348 patients with hypertension from the United Kingdom and Czech Republic, in which adherence was measured in urine and serum, respectively, by LC-MS/MS. That study found younger age, female sex, the number of antihypertensive medications prescribed and prescription of diuretics to be associated with nonadherence [29]. However, in the aforementioned study, the number of antihypertensive medications prescribed was fewer (median 4 and 3, respectively); and BP readings, the number of all medications (hypertensive and nonhypertensive) prescribed, ethnicity, BMI and eGFR were not reported.

The association between younger age and medication nonadherence has been observed in many chronic conditions including hypertension, diabetes, asthma, heart failure and depression [30]. However, the association between age and nonadherence in hypertension is variable with younger age [29,31–33], older age [34] or no association reported [35,36]. Younger patients with busy working lives may have higher unintentional nonadherence. Lifelong treatment for a chronic asymptomatic illness may also be a contributing factor. Conversely, older patients, with
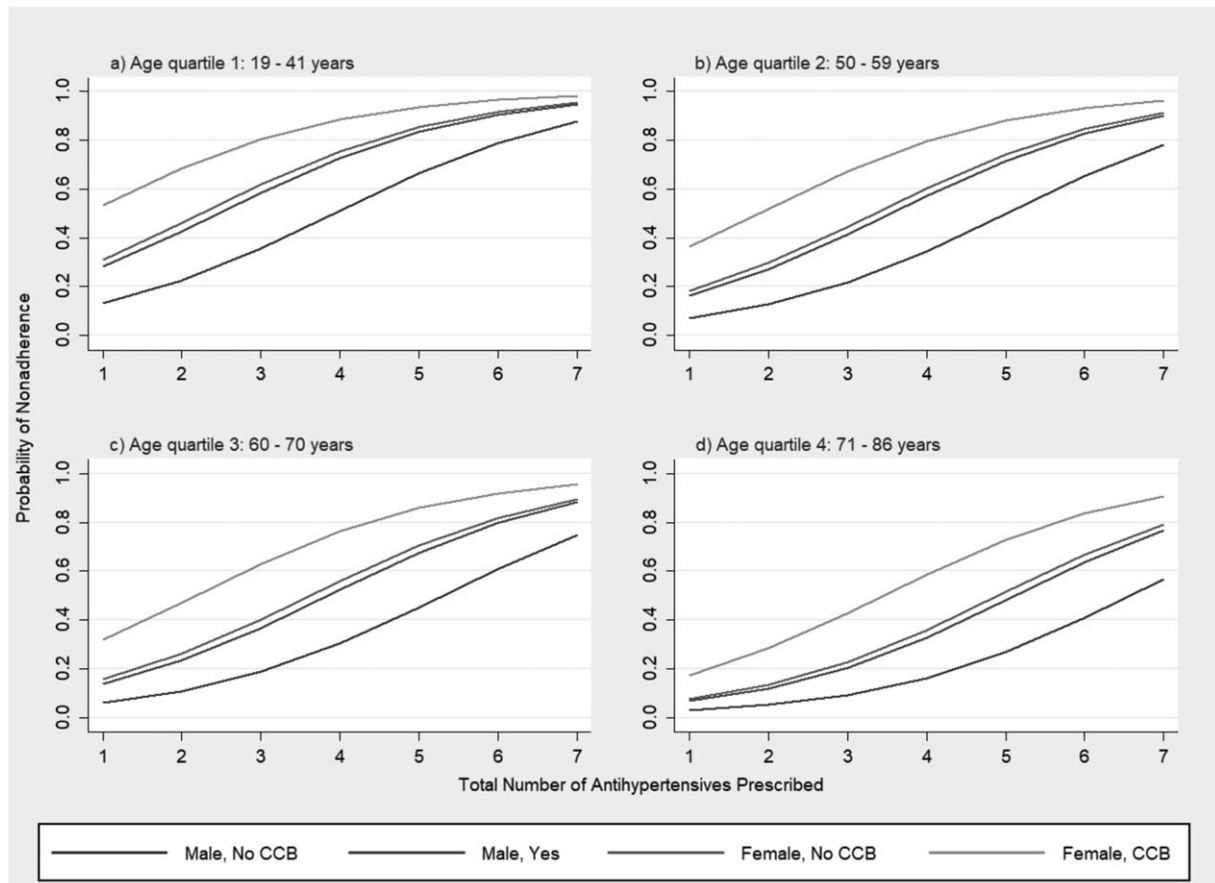
FIGURE 4 Probability of nonadherence by sex and prescription of calcium channel blockers in different age quartiles.

greater burden or severity of illness, are more motivated to adhere, and some may have carers to ensure optimal adherence. Furthermore, these patients may represent a survivor cohort effect, implying successful medication-taking behaviour.

Lower medication adherence among women has been observed in various chronic conditions [37–39] including hypertension [29,32,34,40] The underlying mechanism for this association is unclear, but sex-specific factors may be responsible. Different behavioural attitudes have been observed with more men admitting to forgetting or changing the dosage or think they have recovered from the condition. More women report filling the prescription but not taking the drug, and attribute nonadherence to adverse drug reactions [41]. Whilst sexual dysfunction and BMI of at least 25 kg/m^2 are associated with nonadherence in hypertensive men, dissatisfaction with communication with the healthcare provider and depressive symptoms are associated with lower adherence in women [42].

The most important and novel observation in our study is that nonadherence to antihypertensive treatment was independently associated with two separate measures of polypharmacy, that is, the number of prescribed antihypertensives and the total number of prescribed medications in a cohort with apparent treatment-resistant hypertension. The association between polypharmacy and medication nonadherence has been reported in a number of chronic conditions; including hypertension, type 2 diabetes,

coronary artery disease and after discharge from hospital following inpatient admission; and has been shown to be associated with poorer outcomes [43–48]. Nonadherence is particularly common among community-dwelling elderly individuals who are on multidrug regimens for several comorbid conditions presenting a unique challenge to patients and caregivers, and is a public health concern [49,50]. Limited evidence suggests that de-prescribing may improve medication adherence in this situation [51]. In addition to improving adherence, de-prescribing helps resolution of adverse drug reactions, increases patient engagement with treatment, and reduces medication wastage and cost to the health service [52].

In hypertensive individuals, simplification of treatment regimen has been shown to improve BP control [53]. Indeed, a number of studies in mild-to-moderate hypertension have demonstrated improvement in BP control with single pill fixed-dose combination therapy [54–56], supporting the view that pill burden is an important intervention target for improving long-term medication adherence [40]. This concept has been incorporated into the recent European Society of Cardiology – European Hypertension Society (ESC-ESH) Guidelines on hypertension [57]. However, the evidence in apparent TRH is scanty. A pilot study of 13 patients found a single-pill fixed triple drug combination reduced clinic BP by 22.8/13.6 and 9.3 mmHg in 24-h mean arterial BP after 18 weeks [58]. Larger studies are required to substantiate this.

Previous findings of a highest risk of nonadherence with diuretics [29,59], when compared with other classes of antihypertensives, is not replicated in our logistic regression model. Instead, prescription of a calcium channel blocker (mainly dihydropyridine) was predictive of nonadherence. The reason for this discrepancy is unclear. However, in the metanalysis quoted above [59], the authors suggested that their observation of diuretics being the most common class of antihypertensive associated with nonadherence could not be generalized to those taking at least one agent. Moreover, this meta-analysis excluded cross-sectional studies reporting adherence at a single point in time, making direct comparison with our results inappropriate. A recently published study investigating the contribution of adverse effects on antihypertensive medication nonadherence has demonstrated that both hydrochlorothiazide, a diuretic, and nifedipine, a dihydropyridine calcium channel blocker, are independently associated with nonadherence, attributable to adverse effects [60]. This finding should prompt clinicians to assess the impact of adverse effects and pharmacological interactions of commonly prescribed antihypertensive agents.

Reasons for medication nonadherence are complex and multifactorial. Socioeconomic, health system-related, therapy-related, condition-related and patient-related factors have been implicated [61,62]. Patients' perception of disease and control, treatment-related beliefs, coherence of beliefs from experience with medication, habit strength and pill burden play important roles [35,40]. Longitudinal studies are needed to elucidate the roles of these factors in predicting adherence at various stages of the chronic illness trajectory including that of hypertension.

Our study has a number of limitations. This was a retrospective study based on the demographic and clinical information provided on the request form for urine drug assay. The BP readings used in the analysis were clinic/office BP readings at the point of urine testing; ambulatory readings were not taken at the point of sending the urine sample. Medication doses were not consistently recorded. Adherence was tested only at a single point of time; no conclusion can be drawn on long-term adherence in this cohort. Indeed, adherence testing at a single time point may have overestimated adherence as medication adherence is known to increase as a clinic visit approaches – the so-called 'white-coat adherence' [63]. Finally, there were some missing data, for which we performed a further logistic regression analysis, excluding parameters with missing values, which supported the results of the main model.

The strengths of the study are that the patient sample was drawn from nine hypertension centres across the United Kingdom and the urine tests were carried out at a single toxicological laboratory using a clinically validated, sensitive and specific LC-MS/MS assay. The patient cohort had ethnicity composition reflecting the current British urban population. They had uncontrolled hypertension and were prescribed a median of four antihypertensive drugs each. All patients had white-coat effect and secondary hypertension excluded. To our knowledge, this is the largest reported TRH population to have direct testing for adherence to medication. We believe the results of this study are generalizable to the apparent TRH population in the United Kingdom.

In conclusion, this study adds to the evidence base suggesting nonadherence to prescribed medications is a major cause of apparent resistance to treatment in hypertensive individuals. Prospective longitudinal studies are needed to confirm this. This study also identifies a number of risk factors for nonadherence in this population, which may help to identify patients at risk of medication nonadherence. Of these, pill burden is a modifiable risk factor, which provides an intervention target to improve long-term BP control.

ACKNOWLEDGEMENTS

Conflicts of interest

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