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Relationship between initial therapy and blood pressure control for high-risk hypertension patients in the United Kingdom: a retrospective cohort study from the THIN General Practice Database

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Keywords

Hypertension, combination therapy, diabetes mellitus, kidney disease, cardiovascular disease, The Health Improvement Network (THIN) database, NICE clinical guidelines.

Abstract

Objective: To examine UK practice patterns in treating newly diagnosed hypertension and to determine whether subgroups of high-risk patients are more or less likely to follow particular therapeutic protocols and to reach blood pressure goals.

Design: Retrospective cohort study.

Setting: This study examined adults in The Health Improvement Network (THIN) UK general practice medical records database who were initiated on medication for hypertension.

Participants: 48,131 patients with essential hypertension diagnosed between 2008-2010 who were registered with a participating practice for a minimum of 13 months prior to, and 6 months following, initiation of therapy. We excluded patients with gestational hypertension or secondary hypertension. Patients were classified into risk groups based on blood pressure readings and comorbid conditions.

Primary and secondary outcome measures: Odds of receiving single vs. combination therapy and odds of achieving blood pressure control targets for high- and low-risk patients were assessed using multivariable logistic regression.

Results: The vast majority of patients (95.8%) were initiated on single drug therapy. Patients with high cardiovascular risk (patients with grade 2-3 hypertension or those with high normal/grade 1 hypertension plus at least one cardiovascular condition pre-treatment) had a statistically significant benefit of starting immediately on combination therapy when blood pressure control was the desired goal (OR: 1.23; 95% CI: 1.06–1.42) but, surprisingly, were less likely than patients with no risk factors to receive combination therapy (OR, adjusted: 0.53; 95% CI: 0.47–0.59).

Conclusions: Combination therapy may be indicated for patients with high cardiovascular risk, who accounted for 60.6% of our study population. The NICE guideline CG34 of 2006 (in effect during the study period) recommended starting with single drug class therapy for most patients, and this advice does seem to have been followed even in cases where a more aggressive approach might have been considered.

Strengths and limitations of this study

- This is one of the largest nationally representative studies of hypertension practice and outcomes in the UK.
- We had access to a very large general practice dataset to identify patient risk factors, but without data on inpatient encounters, the proportion of high-risk patients may have been underestimated.
- The dataset benefited from near complete reporting of follow up blood pressure readings after therapy initiation, but the 6 month follow up period precluded analysis of long term blood pressure control outcomes.
- It may be beneficial to extend this analysis using data from 2012 onwards to assess the impact of the updated 2011 NICE guidelines upon choice of therapeutic agents amongst particular subgroups of the population and whether these choices affected outcomes in clinical practice.

INTRODUCTION

Hypertension—generally defined by sustained blood pressure (BP) ≥140/90mm Hg—is one of the most common premorbid conditions contributing to deadly disease in the United Kingdom. The Health Survey for England reported the prevalence of hypertension to be 27.9% in those aged 40–79 years rising to 49.9% in those aged over 80 years. A similarly high prevalence of hypertension is seen in adults in nearly every country throughout the developed world.[1,2]

More than 7% of deaths worldwide are directly attributable to hypertension, exceeding rates for tobacco use and high cholesterol.[3] Hypertension has been estimated to confer a 3–19% increase in the risk of stroke and a 3% increase in the risk of developing heart failure. It may account for 25% of deaths from coronary artery disease. Patients with hypertension and co-morbid diabetes, obesity or hyperlipidemia have been found to be at even higher risk for cardiovascular disease and end-organ damage. Hypertension places an extraordinarily high economic burden on health care systems through the developed world.[2]

At the same time, hypertension is one of the most significant, single, modifiable risk factors associated with cardiovascular disease and stroke, and appropriate treatment has been shown to significantly reduce both morbidity and mortality associated with these conditions. Together with diet and lifestyle modifications, a range of pharmaceutical therapies have been found to be highly effective in controlling hypertension.

Recommended initial therapy for patients with hypertension varies from country to country. In the United Kingdom, physicians are advised to start patients on

monotherapy and add an additional drug only in the case of failure to reach blood pressure goal on an adequate dose of a single drug.[4-5]

The purpose of this study is to examine real world practice in the treatment of newly diagnosed hypertension in the UK, comparing treatment pathways for low and high risk individuals. Our aim is to determine whether particular subgroups of patients (e.g., those with diabetes or renal disease) are more or less likely than others to follow particular therapeutic protocols and to meet immediate blood pressure goals following therapy initiation.

METHODS

To investigate initial therapy for new onset hypertension in the United Kingdom, we acquired patient-level data from The Health Improvement Network ('THIN') over a three year period, from 2008-2010, utilizing a computerised database of anonymised longitudinal medical records covering approximately 500 UK primary care practices.

The THIN database covers 5.7% of the UK population[6] and captures patient demographics and practice enrolment dates, diagnoses, referrals to secondary care, prescriptions, laboratory results and measurements taken during patient visits.[7-8] These data have been used to study patients with hypertension in the past.[9-11]

Approval of the THIN Scheme was granted by the NHS South-East Multi-centre Research Ethics Committee (MREC) in 2002.[12] Per requirements of the MREC, the present study was granted scientific approval by the data vendor's Scientific Review Committee in March 2012. This manuscript was prepared in compliance with the STROBE guidelines for cohort studies.[13]

Study design

We conducted a retrospective cohort study of adults newly treated for hypertension during calendar years 2008-2010. Patients were required to be continuously registered at a practice for a minimum of 19 months during this period.

The study population included adults (ages 18 and older) with newly treated primary (essential) hypertension as identified by a Read diagnosis code in the electronic medical record (EMR) indicating essential hypertension. Patients with gestational hypertension and secondary hypertension were excluded.

Studies have shown that healthcare claims data accurately capture most patients with hypertension using diagnosis codes.[14] This method was chosen rather than use of actual blood pressure readings to define hypertension since it better allows for exclusion of secondary and gestational hypertension as well as hypertensive emergencies and other causes of high blood pressure not associated with primary hypertension.

To identify newly treated hypertension, we imposed a pre-index 'clean' period of a minimum of 13 months during which patients did not receive a prescription for an antihypertensive medication. This period was chosen since well-controlled patients with hypertension may be expected to visit their GP at least annually for follow up. We allowed an extra month in case of delay in scheduling an annual appointment to obtain a prescription renewal.

The index date was the date of the first prescription for an antihypertensive medication following at least 13 months free from such medication at the outset of the study period.

Patients were followed for a period of 6 months after index treatment initiation (post-treatment period) to allow time to observe the effects of treatment on hypertension outcomes.

Exposures, outcomes and covariates

Antihypertensive therapy. Hypertension guidelines recognize five primary drug classes: thiazide/thiazide-like diuretics, beta blockers (BBs), calcium channel blockers (CCBs), ACE inhibitors (ACEIs), and angiotensin receptor blockers (ARBs). This study examined the use of the five primary classes of anti-hypertensive medications, as monotherapy or in combination, as well as other anti-hypertensive drugs used in general practice. Relevant drugs were identified using codes from Chapter 2 of the British National Formulary (BNF).

Blood pressure control outcomes. Systolic and diastolic blood pressure readings were obtained from the EMR. The last recorded measurement during the periods immediately prior to treatment initiation (pre-treatment period) and in the six months following treatment initiation (post-treatment period) were used to categorize patients into hypertension grade, pre- and post-index. A patient was classified into the highest grade appropriate based on either their systolic or diastolic reading.

Blood pressure was defined as 'in control' or 'out of control' in the post-treatment period depending upon blood pressure readings in relation to threshold targets for particular subgroups of patients, where the targets vary depending upon the presence of comorbid conditions (e.g., diabetes and chronic kidney disease, or

CKD). Thresholds used for our study were based on the relatively conservative UK Quality and Outcomes Framework (QOF) targets of 150/90 for patients without CKD or diabetes, 145/85 for individuals who have diabetes but not CKD, and 140/85 for patients with CKD.[15]

Covariates. Independent variables were constructed based upon the index date (patient demographics and socioeconomic status) or pre-index period (lifestyle characteristics and chronic/comorbid conditions).

i. Patient demographics: age (in years) and sex;

ii. Patient lifestyle variables (measured using Read codes recorded during the pre-index study period): tobacco use (defined as current smoker) and overweight/obese status (measured as BMI>=30 or Read code indicating overweight/obese); and

iii. Chronic conditions (measured using Read codes for all diagnoses on record up to the index treatment date): diabetes mellitus, renal disease, cerebrovascular disease, peripheral vascular disease, hyperlipidemia, myocardial infarction and other coronary heart disease.

Risk cohorts

Patients were assigned to risk groups based on a combination of their pre-treatment blood pressure grade and the presence of comorbid conditions. A patient was considered 'high risk' on the basis of potential cardiovascular morbidity if he or she had a pre-treatment hypertension grade of 2 or 3 or if blood pressure was in the high-

normal to mild range in the presence of one or more key cardiovascular conditions. Patients with kidney disease (with or without diabetes) and those with diabetes (without coexisting kidney disease) were also considered 'high risk'. All others were classified as 'low risk'.

Statistical analysis

We employed a mix of descriptive analyses and logistic regression analyses using SAS software, Version 9.3 for Windows.

Simple descriptive statistics were included to illustrate characteristics of the population, initial treatment regimen, prescription switches in the 6 month post-treatment initiation period, and blood pressure control status in the 13 month pre-treatment period and in the 6 month post-treatment period.

Logistic regression models were used to examine the association between patient characteristics and outcomes of interest. Risk groups were identified in the models and separate models were run for each risk group to examine interactions. Missing data were handled by including separate dummy variables in the regression models to indicate that information was not available. All models were subjected to the Hosmer-Lemeshow goodness of-fit test. Since this test may be sensitive to sample size,[16] we also calculated the c-statistic. Effects are expressed as odds ratios (ORs). Statistical significance of independent variables in each model was evaluated at the alpha<0.05 level. Bonferroni correction was used to maintain this familywise error rate in the presence of multiple pair-wise comparisons.

RESULTS

Study population

A total of 48,131 patients were found to meet all study criteria. Just over half of the population was male with a mean age of 57.3 years. **Table 1** summarizes demographic and key lifestyle variables by risk group. One-third of patients had been diagnosed with one or more risk-elevating comorbid conditions (diabetes, renal disease and cardiovascular disease) prior to index treatment initiation. Others were classified as high risk based on pre-treatment blood pressure readings indicating grade 2 or 3 hypertension. We found high rates of overweight/obesity and smoking across groups.

Table 1. Age and sex distribution of the study population (%)

	High Risk Patients				
	Kidney Disease	Diabetes Mellitus	Cardio-vascular*	Low Risk Patients	All Patients
Age, years					
Mean	67.0	56.8	57.1	55.6	57.3
Median	69.0	57.0	57.0	56.0	57.0
Male, percent	42.0%	58.2%	50.9%	50.5%	50.9%
Obese/overweight, percent	61.4%	83.8%	66.4%	65.7%	67.5%
Current tobacco use, percent	20.3%	25.8%	25.1%	23.7%	24.5%
Number of patients	3,060	4,303	29,175	11,593	48,131
% of patients	6.4	8.9	60.6	24.1	100.0

Note (*): The cardiovascular risk group includes patients with grades 2 or 3 hypertension (with or without comorbid cardiovascular disease) prior to treatment initiation and those with 'high normal' or grade 1 hypertension plus one or more cardiovascular conditions.

Index antihypertensive therapy

The vast majority of patients (95.8%) were initiated on single drug therapy. **Table 2** shows the distribution of patients by index treatment pathway and risk cohort. Combination therapy (either fixed dose combination drugs or multiple single agents prescribed on the index date) was highest for patients with renal disease, at 6.0%, and lowest for patients in the cardiovascular risk group (grade 2 or 3 hypertension pre-treatment or those with high-normal or grade 1 hypertension in combination with one or more cardiovascular conditions).

Table 2. Monotherapy versus combination therapy, by risk cohort, n= 48,131 (%)

Antihypertensive Drug Class	Kidney Disease	Diabetes Mellitus	High Risk Cardio-vascular*	Low Risk Patients	All Patients
Combination therapy (FDC or other)	6.0	4.0	3.2	6.3	4.2
Monotherapy					
ACE-Inhibitors	40.3	61.5	43.0	36.6	42.3
ARBs	3.4	3.5	2.2	2.5	2.4
Calcium channel blockers	25.4	16.7	30.8	22.6	27.7
Diuretics	17.2	9.1	15.4	17.8	15.7
Beta Blockers	4.9	3.3	4.4	10.3	5.9
Other antihypertensive drugs	2.8	1.8	1.1	3.9	1.9

Note: Columns may not sum to 100% because of rounding.

Table 3 shows the results of a multivariate logistic regression of the odds of receiving combination therapy as a function of patient characteristics, including risk cohort. The first model included only patient characteristics (other than risk group), the second included risk groups alone, unadjusted for other patient characteristics, and the third model included risk groups adjusted for patient characteristics (excluding pre-treatment hypertension grade which was included in the definition of the cardiovascular risk group). In model 3, we excluded comorbid conditions since the presence of one or more of these conditions is an integral part of the definition of the high risk groups that were included in this model.

Table 3. Odds of receiving combination therapy versus monotherapy as index treatment

Variable	Model 1: Patient Variables only Odds Ratio [95% CI]	Model 2: Risk groups only Odds Ratio [95% CI]	Model 3: Adjusted Odds Ratio [95% CI]
Age cohort			
Age<55			
Age >=55	0.946 [0.848, 1.055]		1.114 [1.004, 1.236]
Sex			
Female			
Male	**1.385 [1.248, 1.537]**		**1.552 [1.404, 1.716]**
Registration with practice			
Existing patient			
New patient	**1.661 [1.301, 2.120]**		**1.715 [1.353, 2.174]**
History of hypertension			
No prior HTN			
Prior episode of HTN	**1.756 [1.580, 1.952]**		**2.144 [1.938, 2.371]**
Lifestyle factors			
Not current smoker			
Current smoker	**1.245 [1.113, 1.394]**		**1.269 [1.138, 1.415]**
Not obese/overweight			

Overweight	0.972 [0.858, 1.102]		0.904 [0.801, 1.020]
Obese	1.073 [0.945, 1.218]		0.956 [0.846, 1.081]
Comorbid conditions			
Diabetes	0.812 [0.680, 0.971]		
Kidney disease	1.123 [0.932, 1.353]		
Coronary heart disease	**2.980 [2.207, 4.024]**		
Cerebrovascular disease	**1.692 [1.397, 2.050]**		
Peripheral vascular disease	0.976 [0.749, 1.270]		
Myocardial infarction	**5.252 [4.498, 6.133]**		
Hyperlipidaemia	0.916 [0.799, 1.050]		
Pre-treatment HTN grade			
Lower than grade 1			
Grade 1	**0.272 [0.230, 0.322]**		
Grade 2	**0.185 [0.157, 0.218]**		
Grade 3	**0.352 [0.299, 0.415]**		
No pre-treatment bp reading	0.857 [0.693, 1.060]		
Risk group			
Diabetes mellitus		**0.639 [0.530, 0.771]**	**0.597 [0.494, 0.721]**
Kidney disease		1.035 [0.864, 1.240]	0.912 [0.758, 1.098]
Cardiovascular		**0.524 [0.469, 0.584]**	**0.527 [0.472, 0.588]**
Low risk			
Number of observations	44,011	44,011	44,011
Hosmer-Lemeshow Goodness-of-Fit	Pass	Pass	Pass
c-statistic	0.74	0.58	0.65

Note: Bold text indicates statistical significance at the alpha=0.05 level on a two-tailed test estimated with stepdown Bonferroni correction of p-values.

Model 1 shows that men, patients who registered with the practice during the study period, those who had an episode of hypertension prior to the study period, and current smokers all had higher odds of receiving initial treatment with combination therapy. Odds of receiving combination therapy were lower, other things equal, among those with higher grade hypertension in the immediate pre-treatment period. However, the association was non-linear. Patients with grade 2 hypertension had the

lowest odds of receiving combination therapy. Patients who did not have a blood pressure reading recorded for the pre-treatment period (3.7% of all patients) were not significantly less likely to receive combination therapy than those who did.

Model 2 shows that patients with diabetes (OR, adjusted: 0.64; 95% CI: 0.53–0.77) and cardiovascular disease (OR, adjusted: 0.52; 95% CI: 0.47–0.58) were both less likely than those with no risk factors to receive combination therapy. Adjusting for demographics and lifestyle factors in Model 3 did not alter our findings.

Blood pressure control

More than two-thirds of patients (66.8%) had grade 2 hypertension or higher prior to treatment, falling to 13.5% in the post-index period (**Table 4**). Low risk patients were, by definition, those who had no worse than grade 1 hypertension prior to treatment and without risk-elevating comorbid conditions (diabetes, renal disease and cardiovascular disease). A shift from grade 2 or 3 hypertension towards grade 1 (or lower) was observed in the follow-up period in all other subjects, including those with cardiovascular conditions (96.4% were classified in grades 2 or 3 pre-treatment vs. 16.3% afterward), diabetes (53.3% vs. 11.5%) and kidney disease (56.1% vs. 10.9%).

To better understand factors affecting treatment success, we modeled the likelihood of achieving blood pressure control following treatment initiation as a function of therapeutic regimen (monotherapy versus combination therapy) controlling for demographics, comorbid conditions and lifestyle variables for all patients plus model variants run separately for low risk and high risk cohorts (**Table 5**). Being older significantly decreases the odds of achieving blood pressure goal for all

patients except those with kidney disease or diabetes. Men with high cardiovascular risk are less likely than women in this group to achieve blood pressure control. Having ever had a prior episode of hypertension treated in the past significantly reduced the odds of achieving control across all patient groups except those with kidney disease. Patients with diabetes (OR: 1.16; 95% CI: 1.09–1.24) and kidney disease (OR: 1.18; 95% CI: 1.09–1.28) were each slightly more likely to achieve blood pressure control than other patients.

Current smokers with cardiovascular health conditions were less likely to reach blood pressure target (OR: 0.87; 95% CI: 0.82–0.92). Obesity reduced the odds of achieving goal for both cardiovascular risk patients (OR: 0.87; 95% CI: 0.82–0.93) and those deemed low risk (OR: 0.86; 95% CI: 0.77–0.95). However, being merely overweight was associated with slightly higher odds of reaching goal among those in the cardiovascular high risk group (OR: 1.11; 95% CI: 1.05–1.18).

Across all patients and risk sub-groups, the odds of achieving blood pressure control fell with increasing hypertension grade. For the full sample of patients we found that starting on combination therapy increased the odds of achieving blood pressure control relative to starting with mono-therapy.

Table 4. Pre- and post-treatment blood pressure readings (%)

Hypertension Grade	Pre-Treatment					Post-Treatment				
	Kidney Disease	Diabetes Mellitus	Cardio-vascular*	Low Risk Patients	All Patients	Kidney Disease	Diabetes Mellitus	Cardio-vascular*	Low Risk Patients	All Patients
Normal (<120/<80)	1.8	1.1	0.0	2.4	0.8	4.7	3.8	2.1	4.1	2.9
Between normal and high-normal (120-134/80-94)	5.9	4.4	0.0	8.8	2.9	22.8	24.8	17.7	23.6	20.1
High-normal (135-139/85-89)	3.4	3.6	0.5	5.3	2.1	14.3	13.6	14.1	15.7	14.4
Grade 1 (140-159/90-99)	29.3	34.8	3.1	70.2	23.8	36.8	36.7	43.9	34.5	40.5
Grade 2 (160-179/100-109)	38.2	37.0	59.3	0.0	41.7	8.0	9.1	12.8	6.7	10.7
Grade 3 (>=180/>=110)	17.9	16.3	37.1	0.0	25.1	2.9	2.4	3.5	1.3	2.8
No reading	3.5	2.8	0.0	13.3	3.7	10.7	9.6	6.0	14.2	8.6

Note (*): The cardiovascular risk group includes patients with grades 2 or 3 hypertension (with or without comorbid cardiovascular disease) prior to treatment initiation and those with 'high normal' or grade 1 hypertension plus one or more cardiovascular conditions.

Table 5. Odds of achieving blood pressure control in the post-treatment period as a function of treatment regimen and risk factors (95% CI in parentheses)

Variable	Kidney Disease	Diabetes Mellitus	Cardiovascular*	Low Risk Patients	All Patients
Age cohort					
Age<=55					
Age >55	0.897 [0.727, 1.107]	0.854 [0.744, 0.980]	**0.770 [0.730, 0.812]**	**0.785 [0.723, 0.853]**	**0.789 [0.757, 0.822]**
Sex					
Female					
Male	1.016 [0.867, 1.191]	0.942 [0.823, 1.077]	**0.797 [0.757, 0.839]**	0.918 [0.846, 0.996]	**0.851 [0.818, 0.886]**
Registration with practice					
Existing patient					
New patient	1.103 [0.675, 1.800]	1.260 [0.898, 1.769]	1.053 [0.908, 1.221]	0.922 [0.743, 1.143]	1.032 [0.923, 1.154]
History of hypertension					
No prior HTN					
Prior episode of HTN	0.790 [0.673, 0.928]	**0.715 [0.617, 0.829]**	**0.878 [0.828, 0.931]**	**0.847 [0.772, 0.928]**	**0.843 [0.806, 0.882]**
Comorbid conditions					
Diabetes	1.061 [0.845, 1.331]				**1.161 [1.085, 1.242]**
Kidney disease					**1.180 [1.088, 1.280]**
Coronary heart disease	1.133 [0.685, 1.875]	0.731 [0.317, 1.686]	1.134 [0.841, 1.530]	1.605 [0.859, 3.001]	1.138 [0.909, 1.425]
Cerebrovascular disease	1.034 [0.776, 1.378]	1.318 [0.936, 1.858]	**1.254 [1.090, 1.443]**	**1.810 [1.314, 2.493]**	**1.278 [1.153, 1.416]**
Peripheral vascular disease	0.797 [0.585, 1.085]	1.097 [0.905, 1.330]	1.168 [0.987, 1.382]	0.715 [0.417, 1.226]	1.056 [0.944, 1.182]
Myocardial infarction	1.103 [0.804, 1.513]	**1.785 [1.210, 2.633]**	1.161 [0.976, 1.382]	**1.785 [1.349, 2.363]**	**1.315 [1.166, 1.482]**
Hyperlipidaemia	0.976 [0.818, 1.165]	1.081 [0.932, 1.255]	1.086 [1.012, 1.166]	1.106 [0.991, 1.233]	**1.078 [1.023, 1.136]**
Lifestyle factors					
Not current smoker					
Current smoker	1.180 [0.973, 1.431]	0.936 [0.805, 1.088]	**0.871 [0.821, 0.924]**	0.998 [0.908, 1.098]	**0.923 [0.882, 0.967]**
Not obese/overweight					

Overweight	0.976 [0.813, 1.171]	1.199 [0.981, 1.465]	**1.112 [1.046, 1.183]**	1.074 [0.974, 1.184]	**1.098 [1.046, 1.152]**
Obese	0.974 [0.796, 1.191]	0.971 [0.802, 1.177]	**0.874 [0.820, 0.930]**	**0.857 [0.774, 0.948]**	**0.881 [0.838, 0.925]**
Pre-treatment HTN grade					
Lower than grade 1					
Grade 1	0.740 [0.547, 1.001]	**0.556 [0.426, 0.727]**	**0.516 [0.328, 0.812]**	**0.589 [0.519, 0.669]**	**0.583 [0.527, 0.644]**
Grade 2	**0.416 [0.309, 0.559]**	**0.343 [0.263, 0.448]**	**0.321 [0.206, 0.501]**		**0.374 [0.339, 0.413]**
Grade 3	**0.299 [0.216, 0.414]**	**0.184 [0.137, 0.248]**	**0.201 [0.129, 0.314]**		**0.234 [0.211, 0.259]**
No pre-treatment bp reading	0.448 [0.263, 0.765]	**0.330 [0.204, 0.532]**		**0.333 [0.283, 0.391]**	**0.340 [0.295, 0.392]**
Initial therapy					
Monotherapy					
Combination therapy	1.378 [0.981, 1.937]	1.138 [0.788, 1.644]	**1.228 [1.061, 1.421]**	1.118 [0.928, 1.348]	**1.213 [1.093, 1.346]**
Number of observations	2,732	3,892	27,438	9,949	44,011
Hosmer-Lemeshow Goodness-of-Fit	Fail	Pass	Pass	Pass	Pass
C-statistic	0.62	0.64	0.59	0.59	0.62

Note: Statistical significance at the alpha=0.05 level on a two-tailed test estimated with stepdown Bonferroni correction of p-values.
Note (*): The cardiovascular risk group includes patients with grades 2 or 3 hypertension (with or without comorbid cardiovascular disease) prior to treatment initiation and those with 'high normal' or grade 1 hypertension plus one or more cardiovascular conditions.

DISCUSSION

This study of a large cohort of patients with newly treated hypertension in the UK found that a majority had risk factors, including comorbid cardiovascular conditions, diabetes and/or kidney disease alone or in combination with index blood pressure readings consistent with grade 2 or 3 hypertension. Many were also current smokers and/or were overweight or obese.

Conservative versus aggressive therapy for high risk patients

Combination therapy may be indicated for patients with grade 2 or 3 hypertension or high normal/grade 1 hypertension plus at least one cardiovascular condition. Although it is commonly thought that combination therapy is also necessary to attain blood pressure control in patients with diabetes or kidney disease, our results showed that it was not a statistically significant predictor of reaching blood pressure goals in these subgroups. Based on our findings, 60.6% of patients in our study population might have benefited more from initiation on multiple drugs. However, given that past NICE guidelines promulgate initiation on monotherapy, it is perhaps not surprising that we found that only 4.2% of patients started on combination therapy. The patients who may benefit most (e.g., those in our cardiovascular high risk group) were actually the least likely to be prescribed combination therapy (3.2% compared with 6.3% of patients with no risk factors), either in the form of fixed dose combination pills or multi-drug class prescriptions.

Following the recently published SPRINT study (a randomized trial of intensive versus standard blood pressure control among patients with cardiovascular risk

factors),[17] which was halted early owing to the finding that patients in the intensive arm (with goal systolic BP <120 mm Hg) had lower rates of major cardiac events and lower rates of all-cause mortality than patients in the standard arm, it is likely that target blood pressure readings for patients with cardiovascular risk factors will be lowered in the future. Multidrug therapy may prove helpful to many patients aiming to meet the lower blood pressure target threshold.

New blood pressure goals and recommended therapies for patients with diabetes or kidney disease

Controlling blood pressure for subgroups of patients with diabetes and/or chronic kidney disease is particularly important as the combination of hypertension with either condition is associated with greatly increased risk of morbidity. Our multivariable analysis showed that patients with diabetes or chronic kidney disease were slightly more likely than other patients to meet the blood pressure target of <140/90. Although at the time that our data were collected UK patients with these conditions had been encouraged to aim for even lower readings, more recent data suggest that meeting the general threshold may be preferable, prompting changes in both European and UK guidelines.

It has been found that reduction of systolic blood pressure below 130 mm Hg is quite difficult to achieve for patients with diabetes, and a reappraisal of European guidelines undertaken in 2009, and the most recent ESH-ESC guideline, backed off from recommendations of lower systolic BP goals for patients with diabetes and renal

disease owing to a lack of clinical trial evidence of benefit from attaining the lower thresholds in these special populations.[18-19]

Recently adopted NICE guidelines specific to patients with diabetes, set target blood pressure at or below140/90 unless there is kidney, eye or cardiovascular damage, in which case the goal is to keep blood pressure <130/80 mm Hg. Caution is urged in treating diabetic patients too aggressively since the risk of adverse side effects, such as orthostatic hypotension, associated with use of antihypertensive medications is raised in patients with autonomic neuropathy. Some drug classes are not recommended owing to microvascular complications or metabolic problems. In general, ACEIs or ARBs are preferred as initial therapy,[20] and we found that together these drugs as monotherapy accounted for 65% of index treatment regimens chosen for patients with diabetes. Although patients with diabetes had the lowest percentage use of diuretics of all risk groups, this drug class still accounted for 9.1% of initial therapy.

For patients with chronic kidney disease, blood pressure targets do not differ from other patients. However, when the albumin/creatinine ratio (ACR)≥30 mg/mmol, ACEIs or ARBs are the recommended therapy. Other treatment pathways may be selected in the presence of hypertension with ACR<30 mg/mmol.[21] We were not able to evaluate ACR levels. However, we did find that ACEs and ARBs accounted for 43.7% of index treatments offered to patients with kidney disease.

Strengths and Limitations of the Study Design and Data

This study was based on observations of a large, population-based sample of patients in real world practice conditions. Retrospective analyses based on medical records that were collected for administrative purposes rather than for research are subject to limitations inherent in the data, including potentially incomplete reporting of certain data elements. In particular, lack of complete data from inpatient and other encounter types may have limited our ability to identify high risk patients. Given that UK GPs act as gatekeepers for specialist and non-emergency inpatient care, data are missing far less frequently than in other health data systems in the US and Europe. Nevertheless, the prevalence of chronic conditions may be underestimated since diagnoses are not recorded at every visit. We attempted to mitigate this problem by counting all recorded diagnoses available for each patient, including conditions reported prior to the start of the study period.

Guidelines have recently been updated and it would be interesting to assess whether this has had an impact on how newly diagnosed patients with hypertension are treated. Replicating these analyses for the period 2012 onward to assess potential changes in practice patterns under the more recent NICE[5,20-21] and European[18] guidelines is warranted.

Conclusion

We report mixed findings on the adherence of physicians to best practice guidelines for special populations of high risk patients in the UK. The NICE guideline CG34 of

2006—in effect during the study period—recommended to start conservatively with single drug class therapy for most patients and this seems to have been followed even in cases where a more aggressive approach might have been considered. One issue this study raised is that most patients seen in UK general practice are in fact high risk patients. Patients with diabetes, for whom there are benefits to deferring a move to multidrug therapy, were found to be less likely than patients with no risk factors to be treated aggressively initially. However, patients with extremely high blood pressure readings (grade 2 or 3) were also less likely than those with lower than grade 1 hypertension readings and no other risk factors to receive aggressive early therapy. The message that treatment must be tailored to the patient's individual risk profile needs greater emphasis, and this may mean backing away from the historically conservative approach taken by NICE except in the case of patients with lower grade hypertension and no other risk factors.

Contributors SW, AJ, JP, and TT contributed to the conception or design of the work. SW was involved in data acquisition and carried out data analysis and interpretation. SW and TT participated in the drafting of the article and were responsible for the critical revision of the article. SW, AJ, JP and TT gave final approval of the version to be published.

Competing interests Jorge Puelles is employed by Takeda Europe Ltd. At the time of the study and during manuscript development, Attila Juhasz was an employee of Takeda Europe, Ltd., Clinical Sciences. Sharada Weir received consulting fees from PHMR Ltd. to conduct the analyses and prepare the manuscript but has no ongoing conflict of interest in relation to the research results. Travis Tierney has no personal, financial or institutional conflicts of interests associated with this work, nor has he ever received any fees or monetary compensation of any kind for his authorship contribution.

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **[See the title, page 1, and 'design' section of the abstract, page 2]**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **[See 'primary and secondary outcome measures' and 'results' sections of abstract, page 2]**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **[pages 4-5]**
Objectives	3	State specific objectives, including any prespecified hypotheses **[final paragraph of the 'introduction' section, page 5]**
Methods		
Study design	4	Present key elements of study design early in the paper **[pages 5-9]**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **[page 5]**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **[pages 6-7]**
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed **[n/a]**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **[pages 7-8]**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **[pages 7-8]**
Bias	9	Describe any efforts to address potential sources of bias **[See page 8 with more information included in the 'study limitations' section, page 22]**
Study size	10	Explain how the study size was arrived at **[See page 6 and 'study population' under 'results', page 9]**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **[page 9]**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **[page 9]**
		(*b*) Describe any methods used to examine subgroups and interactions **[pages 8-9]**
		(*c*) Explain how missing data were addressed **[page 9]**
		(*d*) If applicable, explain how loss to follow-up was addressed **[n/a, the study inclusion criteria stipulated that all patients were required to have 6 months follow up in the data]**
		(*e*) Describe any sensitivity analyses **[n/a]**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **[page 10]**
		(b) Give reasons for non-participation at each stage **[n/a]**
		(c) Consider use of a flow diagram **[n/a]**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **[page 10 and table 1]**

		(b) Indicate number of participants with missing data for each variable of interest **[Table 4]**
		(c) Summarise follow-up time (eg, average and total amount) **[n/a, study restricted to 6 month follow up period available for all participants]**
Outcome data	15*	Report numbers of outcome events or summary measures over time **[Tables 2 and 4]**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **[Tables 3 and 5]**
		(*b*) Report category boundaries when continuous variables were categorized **[Tables 3-5]**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **[n/a]**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **[n/a]**
Discussion		
Key results	18	Summarise key results with reference to study objectives **[Page 19]**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **[Page 22]**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **[Pages 19-21]**
Generalisability	21	Discuss the generalisability (external validity) of the study results **[Page 22]**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **[See 'funding' and 'competing interests' data uploaded with submission]**

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Relationship between initial therapy and blood pressure control for high-risk hypertension patients in the United Kingdom: a retrospective cohort study from the THIN General Practice Database

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Relationship between initial therapy and blood pressure control for high-risk hypertension patients in the United Kingdom: a retrospective cohort study from the THIN General Practice Database

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Keywords

Hypertension, combination therapy, diabetes mellitus, kidney disease, cardiovascular disease, The Health Improvement Network (THIN) database, NICE clinical guidelines.

Abstract

Objective: To examine UK practice patterns in treating newly diagnosed hypertension and to determine whether subgroups of high-risk patients are more or less likely to follow particular therapeutic protocols and to reach blood pressure goals.

Design: Retrospective cohort study.

Setting: This study examined adults in The Health Improvement Network (THIN) UK general practice medical records database who were initiated on medication for hypertension.

Participants: 48,131 patients with essential hypertension diagnosed between 2008-2010 who were registered with a participating practice for a minimum of 13 months prior to, and 6 months following, initiation of therapy. We excluded patients with gestational hypertension or secondary hypertension. Patients were classified into risk groups based on blood pressure readings and comorbid conditions.

Primary and secondary outcome measures: Odds of receiving single vs. fixed- or free-drug combination therapy and odds of achieving blood pressure control were assessed using multivariable logistic regression.

Results: The vast majority of patients (95.8%) were initiated on single drug therapy. Patients with high cardiovascular risk (patients with grade 2-3 hypertension or those with high normal/grade 1 hypertension plus at least one cardiovascular condition pre-treatment) had a statistically significant benefit of starting immediately on combination therapy when blood pressure control was the desired goal (OR: 1.23; 95% CI: 1.06–1.42) but, surprisingly, were less likely than patients with no risk factors to receive combination therapy (OR, adjusted: 0.53; 95% CI: 0.47–0.59).

Conclusions: Combination therapy may be indicated for patients with high cardiovascular risk, who accounted for 60.6% of our study population. The NICE guideline CG34 of 2006 (in effect during the study period) recommended starting with single drug class therapy for most patients, and this advice does seem to have been followed even in cases where a more aggressive approach might have been considered.

Strengths and limitations of this study

- This is one of the largest nationally representative studies of hypertension practice and outcomes in the UK.
- We had access to a very large general practice dataset to identify patient risk factors, but without data on inpatient encounters, the proportion of high-risk patients may have been underestimated.
- The dataset benefited from near complete reporting of follow up blood pressure readings after therapy initiation, but the 6 month follow up period precluded analysis of long term blood pressure control outcomes.
- It may be beneficial to extend this analysis using data from 2012 onwards to assess the impact of the updated 2011 NICE guidelines upon choice of therapeutic agents amongst particular subgroups of the population and whether these choices affected outcomes in clinical practice.

INTRODUCTION

Hypertension—generally defined by sustained blood pressure (BP) ≥140/90mm Hg—is one of the most common premorbid conditions contributing to deadly disease in the United Kingdom. The Health Survey for England reported the prevalence of hypertension to be 27.9% in those aged 40–79 years rising to 49.9% in those aged over 80 years. A similarly high prevalence of hypertension is seen in adults in nearly every country throughout the developed world.[1,2]

More than 7% of deaths worldwide are directly attributable to hypertension, exceeding rates for tobacco use and high cholesterol.[3] Hypertension has been estimated to confer a 3–19% increase in the risk of stroke and a 3% increase in the risk of developing heart failure. It may account for 25% of deaths from coronary artery disease.[2] Patients with hypertension and co-morbid diabetes, obesity or hyperlipidemia have been found to be at even higher risk for cardiovascular disease and end-organ damage.[4] Hypertension places an extraordinarily high economic burden on health care systems through the developed world.[2,5]

At the same time, hypertension is one of the most significant, single, modifiable risk factors associated with cardiovascular disease and stroke, and appropriate treatment has been shown to significantly reduce both morbidity and mortality associated with these conditions.[2,6,7] Together with diet and lifestyle modifications, a range of pharmaceutical therapies have been found to be highly effective in controlling hypertension.[8]

Recommended initial therapy for patients with hypertension varies from country to country. In the United Kingdom, physicians are advised to start patients on

monotherapy and add an additional drug only in the case of failure to reach blood pressure goal on an adequate dose of a single drug.[9,10] European guidelines have for more than a decade emphasized the importance of considering additional cooccurring cardiovascular, renal and metabolic conditions when initiating treatment for hypertension, recommending different strategies depending upon overall cardiovascular risk.[11]

The purpose of this study is to examine real world practice in the treatment of newly diagnosed hypertension in the UK, comparing treatment pathways for low and high risk individuals. Our aim is to determine whether particular subgroups of patients (e.g., those with diabetes, renal disease, or additional cardiovascular risk factors) are more or less likely than others to follow particular therapeutic protocols and to meet immediate blood pressure goals following therapy initiation.

METHODS

To investigate initial therapy for new onset hypertension in the United Kingdom, we acquired patient-level data from The Health Improvement Network ('THIN') over a three year period, from 2008-2010, utilizing a computerised database of anonymised longitudinal medical records covering approximately 500 UK primary care practices.

The THIN database covers 5.7% of the UK population[12] and captures patient demographics and practice enrolment dates, diagnoses, referrals to secondary care, prescriptions, laboratory results and measurements taken during patient visits.[13,14] These data have been used to study patients with hypertension in the past.[15-17]

Approval of the THIN Scheme was granted by the NHS South-East Multi-centre Research Ethics Committee (MREC) in 2002.[18] Per requirements of the MREC, the present study was granted scientific approval by the data vendor's Scientific Review Committee in March 2012. The study protocol is available as a web supplement to this article. This manuscript was prepared in compliance with the STROBE guidelines for cohort studies.[19]

Study design

We conducted a retrospective cohort study of adults newly treated for hypertension during calendar years 2008-2010. Patients were required to be continuously registered at a practice for a minimum of 19 months during this period.

The study population included adults (ages 18 and older) with newly treated primary (essential) hypertension as identified by a Read diagnosis code in the electronic medical record (EMR) indicating essential hypertension. Patients with gestational hypertension and secondary hypertension were excluded.

We used diagnosis codes, rather than use of actual blood pressure readings, to define hypertension since that approach better allows for exclusion of secondary and gestational hypertension as well as hypertensive emergencies and other causes of high blood pressure not associated with primary hypertension.

To identify newly treated hypertension, we imposed a pre-index 'clean' period of a minimum of 13 months during which patients did not receive a prescription for an antihypertensive medication. This period was chosen since well-controlled patients with hypertension may be expected to visit their general practitioner (GP) at least

annually for follow up. We allowed an extra month in case of delay in scheduling an annual appointment to obtain a prescription renewal.

The index date was the date of the first prescription for an antihypertensive medication following at least 13 months free from such medication at the outset of the study period.

Patients were followed for a period of 6 months after index treatment initiation (post-treatment period) to allow time to observe the effects of treatment on hypertension outcomes.

Exposures, outcomes and covariates

Antihypertensive therapy. Hypertension guidelines recognize five primary drug classes: thiazide/thiazide-like diuretics, beta blockers (BBs), calcium channel blockers (CCBs), ACE inhibitors (ACEIs), and angiotensin receptor blockers (ARBs). This study examined the use of the five primary classes of anti-hypertensive medications, as monotherapy or in combination, as well as other anti-hypertensive drugs used in general practice. Relevant drugs were identified using codes from Chapter 2 of the British National Formulary (BNF).

Blood pressure control outcomes. Systolic and diastolic blood pressure readings were obtained from the EMR. The last recorded measurement during the periods immediately prior to treatment initiation (pre-treatment period) and in the six months following treatment initiation (post-treatment period) were used to categorize patients into hypertension grade, pre- and post-index. A patient was classified into the

highest grade appropriate based on either their systolic or diastolic reading. Blood pressure was defined as 'in control' or 'out of control' in the post-treatment period depending upon blood pressure readings in relation to the threshold target recommended by NICE of 140/90 .

Covariates. Independent variables were constructed based upon the index date (patient demographics and socioeconomic status) or pre-index period (lifestyle characteristics and chronic/comorbid conditions).

i. Patient demographics: age (in years) and sex;

ii. Patient lifestyle variables (measured using Read codes recorded during the pre-index study period): tobacco use (defined as current smoker) and overweight/obese status (measured as BMI>=30 or Read code indicating overweight/obese); and

iii. Chronic conditions (measured using Read codes for all diagnoses on record up to the index treatment date): diabetes mellitus, renal disease, coronary heart disease (not including myocardial infarction), cerebrovascular disease, peripheral vascular disease, myocardial infarction or hyperlipidemia.

Risk cohorts

Patients were assigned to risk groups based on a combination of their pre-treatment blood pressure grade and the presence of comorbid conditions following criteria outlined by Mancia and colleagues (2013) in their guidelines for management of hypertension.[11] A patient was considered 'high risk' on the basis of potential

cardiovascular morbidity if he or she had a pre-treatment hypertension grade of 2 or 3 or if blood pressure was in the high-normal to mild range in the presence of one or more key cardiovascular conditions (i.e., coronary heart disease, cerebrovascular disease, peripheral vascular disease, myocardial infarction or hyperlipidemia). Patients with kidney disease (with or without diabetes) and those with diabetes (without coexisting kidney disease) were also considered 'high risk'. All others were classified as 'low risk'.

Missing data

UK medical records typically provide nearly complete data for the key study variables identified here. The UK "Quality and Outcomes Framework",[20] introduced in 2004, provides financial incentives for UK general practitioners to appropriately document important metrics and meet selected quality process and outcome goals. Physicians are paid incentive bonuses for keeping a registry of patients with hypertension being treated in their practice and for recording blood pressure in hypertensive patients every 9 months, at a minimum. For patients with diabetes or kidney disease, additional incentives are offered to regularly monitor blood pressure regardless of whether hypertension has been diagnosed. Incentives are also provided for keeping a registry of patients with BMI>=30 in the prior 15 months and for recording smoking status among patient with hypertension or other cardiovascular or metabolic conditions.

For the purposes of analyses, continuous variables (such as BMI) were recoded into categories. Where data were missing, the patient was assumed to fall into the

reference category. The exception was blood pressure recordings, where we created a separate category for missing data.

Statistical analysis

We employed a mix of descriptive analyses and logistic regression analyses using SAS software, Version 9.3 for Windows.

Simple descriptive statistics were included to illustrate characteristics of the population, initial treatment regimen, prescription switches in the 6 month post-treatment initiation period, and blood pressure control status in the 13 month pre-treatment period and in the 6 month post-treatment period.

Logistic regression models were used to examine the association between patient characteristics and outcomes of interest. Risk groups were identified in the models and separate models were run for each risk group to examine interactions. Analyses were restricted to patients who had follow-up blood pressure recorded as this was necessary to evaluate the outcome of blood pressure control. All models were subjected to the Hosmer-Lemeshow goodness of-fit test. Since this test may be sensitive to sample size,[21] we also calculated the c-statistic. Effects are expressed as odds ratios (ORs). Statistical significance of independent variables in each model was evaluated at the alpha<0.05 level. Bonferroni correction was used to maintain this familywise error rate in the presence of multiple pair-wise comparisons.

A sensitivity analysis was performed to assess the potential impact of missing data on blood pressure readings. The blood pressure control regression analysis was re-run twice for each risk group and for all patients: under the first scenario, we

assumed that all patients with missing blood pressure readings had achieved blood pressure control following treatment; under the second scenario, we assumed that they had not.

RESULTS

Study population

A total of 48,131 patients were found to meet all study criteria. Just over half of the population was male with a mean age of 57.3 years. **Table 1** summarizes demographic and key lifestyle variables by risk group. One-third of patients had been diagnosed with one or more risk-elevating comorbid conditions (diabetes, renal disease and cardiovascular disease) prior to index treatment initiation. Others were classified as high risk based on pre-treatment blood pressure readings indicating grade 2 or 3 hypertension. We found high rates of overweight/obesity and smoking across groups.

Index antihypertensive therapy

The vast majority of patients (95.8%) were initiated on single drug therapy. **Table 2** shows the distribution of patients by index treatment pathway and risk cohort. Combination therapy (either fixed dose combination drugs or multiple single agents prescribed on the index date) was highest for patients with renal disease, at 6.0%, and lowest for patients in the cardiovascular risk group (grade 2 or 3 hypertension pre-treatment or those with high-normal or grade 1 hypertension in combination with one or more cardiovascular conditions). The most common drug class used in monotherapy, across all risk classes, was ACE-inhibitors, followed by calcium channel blockers.

Table 1. Age and sex distribution of the study population (%)

	High Risk Patients			Low Risk Patients	All Patients
	Kidney Disease	Diabetes Mellitus	Cardio-vascular*		
Age, years					
Mean	67.0	56.8	57.1	55.6	57.3
Median	69.0	57.0	57.0	56.0	57.0
Male, percent	42.0%	58.2%	50.9%	50.5%	50.9%
Obese/overweight, percent	61.4%	83.8%	66.4%	65.7%	67.5%
Current tobacco use, percent	20.3%	25.8%	25.1%	23.7%	24.5%
Number of patients	3,060	4,303	29,175	11,593	48,131
% of patients	6.4	8.9	60.6	24.1	100.0

Note (*): The cardiovascular risk group includes patients with grades 2 or 3 hypertension (with or without comorbid cardiovascular disease) prior to treatment initiation and those with 'high normal' or grade 1 hypertension plus one or more cardiovascular conditions (i.e., coronary heart disease, cerebrovascular disease, peripheral vascular disease, myocardial infarction or hyperlipidemia).

Table 2. Monotherapy versus fixed- or free-drug combination therapy, by risk cohort, n= 48,131 (%)

Antihypertensive Drug Class	Kidney Disease	Diabetes Mellitus	High Risk Cardio-vascular*	Low Risk Patients	All Patients
Combination therapy	6.0	4.0	3.2	6.3	4.2
Monotherapy					
ACE-Inhibitors	40.3	61.5	43.0	36.6	42.3
ARBs	3.4	3.5	2.2	2.5	2.4
Calcium channel blockers	25.4	16.7	30.8	22.6	27.7
Diuretics	17.2	9.1	15.4	17.8	15.7
Beta Blockers	4.9	3.3	4.4	10.3	5.9
Other antihypertensive drugs	2.8	1.8	1.1	3.9	1.9

Note: Columns may not sum to 100% because of rounding.

Table 3 shows the results of a multivariate logistic regression of the odds of receiving combination therapy as a function of patient characteristics, including risk cohort. The first model included only patient characteristics (other than risk group), the second included risk groups alone, unadjusted for other patient characteristics, and the third model included risk groups adjusted for patient characteristics (excluding pre-treatment hypertension grade which was included in the definition of the cardiovascular risk group). In model 3, we excluded comorbid conditions since the presence of one or more of these conditions is an integral part of the definition of the high risk groups that were included in this model.

Table 3. Odds of receiving fixed- or free-drug combination therapy versus monotherapy as index treatment

Variable	Model 1: Patient Variables only Odds Ratio [95% CI]	Model 2: Risk groups only Odds Ratio [95% CI]	Model 3: Adjusted Odds Ratio [95% CI]
Age cohort			
Age<55			
Age >=55	0.946 [0.848, 1.055]		1.114 [1.004, 1.236]
Sex			
Female			
Male	**1.385 [1.248, 1.537]**		**1.552 [1.404, 1.716]**
Registration with practice			
Existing patient			
New patient	**1.661 [1.301, 2.120]**		**1.715 [1.353, 2.174]**
History of hypertension			
No prior hypertension			
Prior episode of hypertension	**1.756 [1.580, 1.952]**		**2.144 [1.938, 2.371]**
Lifestyle factors			
Not current smoker			
Current smoker	**1.245 [1.113, 1.394]**		**1.269 [1.138, 1.415]**
Not obese/overweight			
Overweight	0.972 [0.858, 1.102]		0.904 [0.801, 1.020]
Obese	1.073 [0.945, 1.218]		0.956 [0.846, 1.081]
Comorbid conditions			
Diabetes	0.812 [0.680, 0.971]		
Kidney disease	1.123 [0.932, 1.353]		
Coronary heart disease	**2.980 [2.207, 4.024]**		
Cerebrovascular disease	**1.692 [1.397, 2.050]**		
Peripheral vascular disease	0.976 [0.749, 1.270]		
Myocardial infarction	**5.252 [4.498, 6.133]**		
Hyperlipidaemia	0.916 [0.799, 1.050]		
Pre-treatment hypertenion grade			
Lower than grade 1			
Grade 1	**0.272 [0.230, 0.322]**		
Grade 2	**0.185 [0.157, 0.218]**		
Grade 3	**0.352 [0.299, 0.415]**		

No pre-treatment BP reading	0.857 [0.693, 1.060]		
Risk group			
Diabetes mellitus		**0.639 [0.530, 0.771]**	**0.597 [0.494, 0.721]**
Kidney disease		1.035 [0.864, 1.240]	0.912 [0.758, 1.098]
Cardiovascular		**0.524 [0.469, 0.584]**	**0.527 [0.472, 0.588]**
Low risk			
Number of observations	44,011	44,011	44,011
Hosmer-Lemeshow Goodness-of-Fit	Pass	Pass	Pass
c-statistic	0.74	0.58	0.65

Note: Bold text indicates statistical significance at the alpha=0.05 level on a two-tailed test estimated with stepdown Bonferroni correction of p-values.

Model 1 shows that men, patients who registered with the practice during the study period, those who had an episode of hypertension prior to the study period, and current smokers all had higher odds of receiving initial treatment with combination therapy. Odds of receiving combination therapy were lower, other things equal, among those with higher grade hypertension in the immediate pre-treatment period. However, the association was non-linear. Patients with grade 2 hypertension had the lowest odds of receiving combination therapy. Patients who did not have a blood pressure reading recorded for the pre-treatment period (3.7% of all patients) were not significantly less likely to receive combination therapy than those who did.

Model 2 shows that patients with diabetes (OR, adjusted: 0.64; 95% CI: 0.53–0.77) and cardiovascular disease (OR, adjusted: 0.52; 95% CI: 0.47–0.58) were both less likely than those with no risk factors to receive combination therapy. Adjusting for demographics and lifestyle factors in Model 3 did not alter our findings.

Blood pressure control

More than two-thirds of patients (66.8%) had grade 2 hypertension or higher prior to treatment, falling to 13.5% in the post-index period. Low risk patients were, by definition, those who had no worse than grade 1 hypertension prior to treatment and without risk-elevating comorbid conditions (diabetes, renal disease and cardiovascular disease). A shift from grade 2 or 3 hypertension towards grade 1 (or lower) was observed in the follow-up period in all other subjects, including those with cardiovascular conditions (96.4% were classified in grades 2 or 3 pre-treatment vs. 16.3% afterward), diabetes (53.3% vs. 11.5%) and kidney disease (56.1% vs. 10.9%)(Figure 1).

To better understand factors affecting treatment success, we modeled the likelihood of achieving blood pressure control following treatment initiation as a function of therapeutic regimen (monotherapy versus combination therapy) controlling for demographics, comorbid conditions and lifestyle variables for all patients plus model variants run separately for low risk and high risk cohorts (**Table 4**). Being older significantly decreases the odds of achieving blood pressure goal for all patients except those with kidney disease or diabetes. Men with high cardiovascular risk are less likely than women in this group to achieve blood pressure control. Having ever had a prior episode of hypertension treated in the past significantly reduced the odds of achieving control across all patient groups except those with kidney disease. Patients with diabetes (OR: 1.16; 95% CI: 1.09–1.24) and kidney disease (OR: 1.18; 95% CI: 1.09–1.28) were each slightly more likely to achieve blood pressure control than other patients.

Current smokers with cardiovascular health conditions were less likely to reach blood pressure target (OR: 0.87; 95% CI: 0.82–0.92). Obesity reduced the odds of achieving goal for both cardiovascular risk patients (OR: 0.87; 95% CI: 0.82–0.93) and those deemed low risk (OR: 0.86; 95% CI: 0.77–0.95). However, being merely overweight was associated with slightly higher odds of reaching goal among those in the cardiovascular high risk group (OR: 1.11; 95% CI: 1.05–1.18).

Across all patients and risk sub-groups, the odds of achieving blood pressure control fell with increasing hypertension grade. For the full sample of patients, we found that starting on combination therapy increased the odds of achieving blood pressure control relative to starting with mono-therapy.

We performed a sensitivity analysis to assess the potential impact of missing data on blood pressure readings by re-rerunning the analyses on all patients, first assuming that all patients with missing blood pressure readings had achieved blood pressure control following treatment and, second, assuming that they had not. There were no substantive changes in the coefficients under either scenario, though a few of the covariates (prior hypertension, current smoking status, and overweight BMI) became insignificant under the first scenario assuming that all patients with missing BP recordings had met the blood pressure control goal.

Table 4. Odds of achieving blood pressure control in the post-treatment period as a function of treatment regimen and risk factors (95% CI in parentheses)

Variable	Kidney Disease	Diabetes Mellitus	Cardiovascular*	Low Risk Patients	All Patients
Age cohort					
Age<=55					
Age >55	0.897 [0.727, 1.107]	0.854 [0.744, 0.980]	**0.770 [0.730, 0.812]**	**0.785 [0.723, 0.853]**	**0.789 [0.757, 0.822]**
Sex					
Female					
Male	1.016 [0.867, 1.191]	0.942 [0.823, 1.077]	**0.797 [0.757, 0.839]**	0.918 [0.846, 0.996]	**0.851 [0.818, 0.886]**
Registration with practice					
Existing patient					
New patient	1.103 [0.675, 1.800]	1.260 [0.898, 1.769]	1.053 [0.908, 1.221]	0.922 [0.743, 1.143]	1.032 [0.923, 1.154]
History of hypertension					
No prior hypertension					
Prior episode of hypertension	0.790 [0.673, 0.928]	**0.715 [0.617, 0.829]**	**0.878 [0.828, 0.931]**	**0.847 [0.772, 0.928]**	**0.843 [0.806, 0.882]**
Comorbid conditions					
Diabetes	1.061 [0.845, 1.331]				**1.161 [1.085, 1.242]**
Kidney disease					**1.180 [1.088, 1.280]**
Coronary heart disease	1.133 [0.685, 1.875]	0.731 [0.317, 1.686]	1.134 [0.841, 1.530]	1.605 [0.859, 3.001]	1.138 [0.909, 1.425]
Cerebrovascular disease	1.034 [0.776, 1.378]	1.318 [0.936, 1.858]	**1.254 [1.090, 1.443]**	**1.810 [1.314, 2.493]**	**1.278 [1.153, 1.416]**
Peripheral vascular disease	0.797 [0.585, 1.085]	1.097 [0.905, 1.330]	1.168 [0.987, 1.382]	0.715 [0.417, 1.226]	1.056 [0.944, 1.182]
Myocardial infarction	1.103 [0.804, 1.513]	**1.785 [1.210, 2.633]**	1.161 [0.976, 1.382]	**1.785 [1.349, 2.363]**	**1.315 [1.166, 1.482]**
Hyperlipidaemia	0.976 [0.818, 1.165]	1.081 [0.932, 1.255]	1.086 [1.012, 1.166]	1.106 [0.991, 1.233]	**1.078 [1.023, 1.136]**
Lifestyle factors					
Not current smoker					
Current smoker	1.180 [0.973, 1.431]	0.936 [0.805, 1.088]	**0.871 [0.821, 0.924]**	0.998 [0.908, 1.098]	**0.923 [0.882, 0.967]**

Not obese/overweight					
Overweight	0.976 [0.813, 1.171]	1.199 [0.981, 1.465]	**1.112 [1.046, 1.183]**	1.074 [0.974, 1.184]	**1.098 [1.046, 1.152]**
Obese	0.974 [0.796, 1.191]	0.971 [0.802, 1.177]	**0.874 [0.820, 0.930]**	**0.857 [0.774, 0.948]**	**0.881 [0.838, 0.925]**
Pre-treatment hypertension grade					
Lower than grade 1					
Grade 1	0.740 [0.547, 1.001]	**0.556 [0.426, 0.727]**	**0.516 [0.328, 0.812]**	**0.589 [0.519, 0.669]**	**0.583 [0.527, 0.644]**
Grade 2	**0.416 [0.309, 0.559]**	**0.343 [0.263, 0.448]**	**0.321 [0.206, 0.501]**		**0.374 [0.339, 0.413]**
Grade 3	**0.299 [0.216, 0.414]**	**0.184 [0.137, 0.248]**	**0.201 [0.129, 0.314]**		**0.234 [0.211, 0.259]**
No pre-treatment BP reading	0.448 [0.263, 0.765]	**0.330 [0.204, 0.532]**		**0.333 [0.283, 0.391]**	**0.340 [0.295, 0.392]**
Initial therapy					
Monotherapy					
Combination therapy	1.378 [0.981, 1.937]	1.138 [0.788, 1.644]	**1.228 [1.061, 1.421]**	1.118 [0.928, 1.348]	**1.213 [1.093, 1.346]**
Number of observations	2,732	3,892	27,438	9,949	44,011
Hosmer-Lemeshow Goodness-of-Fit	Fail	Pass	Pass	Pass	Pass
C-statistic	0.62	0.64	0.59	0.59	0.62

Note: Bold text indicates statistical significance at the alpha=0.05 level on a two-tailed test estimated with stepdown Bonferroni correction of p-values.
Note (*): The cardiovascular risk group includes patients with grades 2 or 3 hypertension (with or without comorbid cardiovascular disease) prior to treatment initiation and those with 'high normal' or grade 1 hypertension plus one or more cardiovascular conditions (i.e., coronary heart disease, cerebrovascular disease, peripheral vascular disease, myocardial infarction or hyperlipidemia).

DISCUSSION

This study of a large cohort of patients with newly treated hypertension in the UK found that a majority had risk factors, including comorbid cardiovascular conditions, diabetes and/or kidney disease alone or in combination with index blood pressure readings consistent with grade 2 or 3 hypertension. Many were also current smokers and/or were overweight or obese.

Conservative versus aggressive therapy for high risk patients

Combination therapy may be indicated for patients with grade 2 or 3 hypertension or high normal/grade 1 hypertension plus at least one cardiovascular condition. Although it is commonly thought that combination therapy is also necessary to attain blood pressure control in patients with diabetes or kidney disease, our results showed that it was not a statistically significant predictor of reaching blood pressure goals in these subgroups. Based on our findings, 60.6% of patients in our study population might have benefited more from initiation on multiple drugs. However, given that past NICE guidelines promulgate initiation on monotherapy, it is perhaps not surprising that we found that only 4.2% of patients started on combination therapy. The patients who may benefit most (e.g., those in our cardiovascular high risk group) were actually the least likely to be prescribed combination therapy (3.2% compared with 6.3% of patients with no risk factors), either in the form of fixed dose combination pills or multi-drug class prescriptions.

Following the recently published SPRINT study (a randomized trial of intensive versus standard blood pressure control among patients with cardiovascular risk

factors),[22] which was halted early owing to the finding that patients in the intensive arm (with goal systolic BP <120 mm Hg) had lower rates of major cardiac events and lower rates of all-cause mortality than patients in the standard arm, it is likely that target blood pressure readings for patients with cardiovascular risk factors will be lowered in the future. If so, more aggressive initial therapy for this risk cohort may be recommended.

New blood pressure goals and recommended therapies for patients with diabetes or kidney disease

Controlling blood pressure for subgroups of patients with diabetes and/or chronic kidney disease is particularly important as the combination of hypertension with either condition is associated with greatly increased risk of morbidity.[11] Our multivariable analysis showed that patients with diabetes or chronic kidney disease were slightly more likely than other patients to meet the blood pressure target of <140/90. Although at the time that our data were collected UK patients with these conditions had been encouraged to aim for even lower readings, more recent data suggest that meeting the general threshold may be preferable, prompting changes in both European and UK guidelines.

It has been found that reduction of systolic blood pressure below 130 mm Hg is quite difficult to achieve for patients with diabetes,[11] and a reappraisal of European guidelines undertaken in 2009, and the most recent ESH-ESC guideline, backed off from recommendations of lower systolic BP goals for patients with diabetes and renal

disease owing to a lack of clinical trial evidence of benefit from attaining the lower thresholds in these special populations.[11,23]

Recently adopted NICE guidelines specific to patients with diabetes, set target blood pressure at or below 140/90 unless there is kidney, eye or cardiovascular damage, in which case the goal is to keep blood pressure <130/80 mm Hg. Caution is urged in treating diabetic patients too aggressively since the risk of adverse side effects, such as orthostatic hypotension, associated with use of antihypertensive medications is raised in patients with autonomic neuropathy.[24] Some drug classes are not recommended owing to microvascular complications or metabolic problems. In general, ACEIs or ARBs are preferred as initial therapy,[25] and we found that together these drugs as monotherapy accounted for 65% of index treatment regimens chosen for patients with diabetes. Although patients with diabetes had the lowest percentage use of diuretics of all risk groups, this drug class still accounted for 9.1% of initial therapy.

For patients with chronic kidney disease, blood pressure targets do not differ from other patients. However, when the albumin/creatinine ratio (ACR)≥30 mg/mmol, ACEIs or ARBs are the recommended therapy. Other treatment pathways may be selected in the presence of hypertension with ACR<30 mg/mmol.[26] We were not able to evaluate ACR levels. However, we did find that ACEs and ARBs accounted for 43.7% of index treatments offered to patients with kidney disease.

Strengths and Limitations of the Study Design and Data

This study was based on observations of a large, population-based sample of patients in real world practice conditions. Retrospective analyses based on medical records that were collected for administrative purposes rather than for research are subject to limitations inherent in the data, including potentially incomplete reporting of certain data elements. One key study limitation is that our study population was identified in part using READ codes in the primary care setting only. Some patients with primary hypertension may have been missed or misclassified if READ codes were incorrectly recorded or missing. Evidence is lacking to validate the use of READ codes (versus repeated blood pressure measurements) to identify cases of primary hypertension accurately.

Lack of complete data from inpatient and other encounter types may also have limited our ability to identify high risk patients. Given that UK GPs act as gatekeepers for specialist and non-emergency inpatient care, data are missing far less frequently than in other health data systems in the US and Europe. Nevertheless, the prevalence of chronic conditions may be underestimated since diagnoses are not recorded at every visit. One UK study estimated that more than 25% of myocardial infarction events may be missed using primary care encounters data alone.[27] We attempted to mitigate this problem by counting all recorded diagnoses available for each patient, including conditions reported prior to the start of the study period.

It was not possible to assess medication compliance in our population, since prescription data in medical records indicate the physician's intention, but do not

directly reveal any information regarding patient compliance with prescribed therapies including whether prescriptions were filled. While it was possible to observe changes in prescribed medications, complete information was not available on the reasons for adding or changing medications (i.e., owing to adverse effects or lack of effectiveness). A longer follow up period would be needed to examine the impact of changes in drug therapy (e.g., drug class, dose, fixed- or free drug combinations) on BP control. A longer follow up period would also be required to assess the long-term effect upon blood pressure outcomes of initial therapy choice.

Finally, selection bias may have been introduced in the regression analyses because of the necessity of limiting analysis of blood pressure control to patients who had a follow up blood pressure readings recorded. Missing follow up data on this key variable cannot be assumed to occur at random and may differ by risk cohort. However, the results of our sensitivity analysis suggest that the impact was minimal

Guidelines have recently been updated and it would be interesting to assess whether this has had an impact on how newly diagnosed patients with hypertension are treated. While the NICE guidelines remain conservative, favouring monotherapy initially, key updates included the recommendation to offer antihypertensive drug therapy to patients with stage 2 hypertension, regardless of age, to patients with diabetes or renal disease, and to patients with 10 year cardiovascular risk >=20%.[10] Replicating these analyses for the period 2012 onward to assess potential changes in practice patterns under the more recent NICE[10,25,26] and European[11] guidelines is warranted.

Conclusion

We report mixed findings on the adherence of physicians to best practice guidelines for special populations of high risk patients in the UK. The NICE guideline CG34 of 2006—in effect during the study period—recommended to start conservatively with single drug class therapy for most patients and this seems to have been followed even in cases where a more aggressive approach might have been considered. One issue this study raised is that most patients treated for hypertension in UK general practice are in fact high risk patients. Patients with diabetes, for whom there are benefits to deferring a move to multidrug therapy, were found to be less likely than patients with no risk factors to be treated aggressively initially. However, patients with extremely high blood pressure readings (grade 2 or 3) were also less likely than those with lower than grade 1 hypertension readings and no other risk factors to receive aggressive early therapy. The message that treatment must be tailored to the patient's individual risk profile needs greater emphasis, and this may mean backing away from the historically conservative approach taken by NICE except in the case of patients with lower grade hypertension and no other risk factors.

Contributors: SW, AJ, JP, and TT contributed to the conception or design of the work. SW was involved in data acquisition and carried out data analysis and interpretation. SW, AJ, JP and TT participated in the drafting of the article. SW and TT were responsible for the critical revision of the article. SW, AJ, JP and TT gave final approval of the version to be published.

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Data sharing statement: No additional unpublished data from the study are available.

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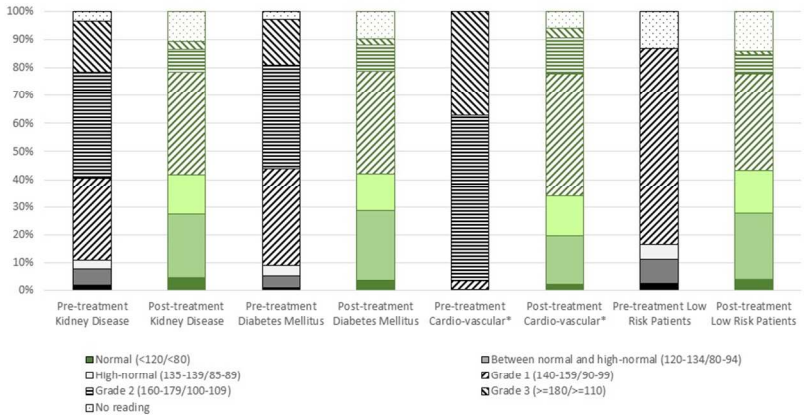

Figure 1. Percentage of patients in each blood pressure control group, pre- and post-treatment initiation, by risk cohort

Note (*): The cardiovascular risk group includes patients with grades 2 or 3 hypertension (with or without comorbid cardiovascular disease) prior to treatment initiation and those with 'high normal' or grade 1 hypertension plus one or more cardiovascular conditions (i.e., coronary heart disease, cerebrovascular disease, peripheral vascular disease, myocardial infarction or hyperlipidemia).

304x171mm (96 x 96 DPI)

THIN Database Study Plan:

Initial Treatment of High Risk Hypertension Patients: ARB Monotherapy versus FDC Therapy

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CONTENTS

1. Motivation

Hypertension is one of the most common diseases in the world, affecting an estimated 20% of the adult population overall. It is also one of the most significant, single, modifiable risk factors in cardiovascular disease, and appropriate treatment has the potential to reduce cardiovascular morbidity and mortality significantly. The treatment pathway for patients with hypertension varies from country to country but European guidelines stress the importance of monotherapy and fixed-dose combination (FDC) therapy (Figure 1). They suggest that most hypertensive patients can only achieve effective BP control by a combination of at least two antihypertensive drugs (Mancia 2009).

Figure 1. Monotherapy versus combination therapy strategies (ESC/ESH Guidelines; Mancia et al. 2007)

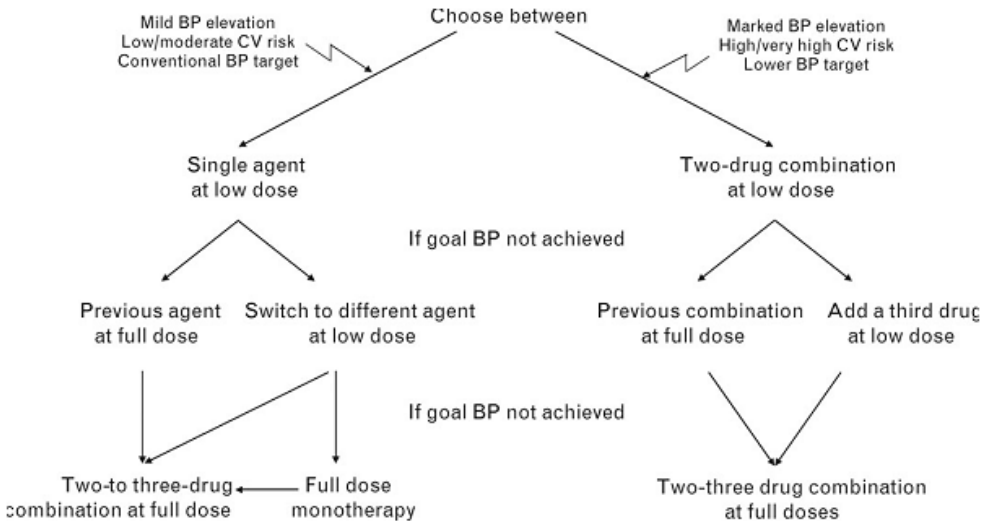


Figure 3 Monotherapy versus combination therapy strategies.

Guidelines and best practices vary for subgroups of patients. Some—such as those who present with higher grade hypertension and/or significant cardiovascular risk factors—may be good candidates for initial FDC therapy. Others—such as those who present with lower grade hypertension and fewer cardiovascular risk factors—may be able to delay movement to FDC, thereby potentially reducing their exposure to negative metabolic effects of some diuretics.

PHMR Associates has been asked by Takeda (Europe) to conduct UK healthcare database analyses to provide a better understanding of the population that may benefit from Azilsartan Medoxomil—a new angiotensin-receptor blocker (ARB)—in the treatment of Essential Hypertension. Identifying a potential initial Azilsartan Medoxomil FDC population and an Azilsartan Medoxomil monotherapy population will highlight care improvement and cost savings opportunities for subgroups of patients and permit more selective marketing to physicians and payers in charge of such patients. More generally, however, the research will provide information on how closely physicians treating high risk patients adhere to guidelines for initial treatment of hypertension and how treatment protocols affect outcomes.

2. Objectives and Specific Aims

Research Objectives

The objectives of the study are: (1) to determine which patients are good candidates for initial treatment with two-drug fixed combination therapy at low dose, rather than monotherapy (e.g., individuals with more severe hypertension), and which patients would benefit from prolonged ARB monotherapy (e.g., patients at risk of developing diabetes); (2) to examine the divergence, if any, between recommended treatment and treatment provided in practice; and (3) to consider the effect upon reaching target blood pressure goals of different treatment regimens for high risk subgroups of patients.

Specific Aims

Specific research questions (D=descriptive analysis; R=regression analysis) include:

a) What percentage of newly diagnosed patients meet guideline-derived criteria for initial treatment with FDC (e.g., patients with high index BP and/or CV risk factors)? What percentage of such patients are treated with initial FDC therapy? (D)

b) What percentage of newly diagnosed patients meet guideline-derived criteria for avoidance of FDC therapy (e.g., patients at risk of diabetes, metabolic syndrome, etc.)? What percentage of such patients are treated with initial ARB/other monotherapy? (D)

c) Among newly diagnosed patients, what percentage change therapy within the first year post-diagnosis? What percentage switch from an ARB to another ARB? What percentage switch from ARB monotherapy directly to FDC therapy? What is the difference in mean time-to-switch between those who try more than one ARB treatment regime and those who switch from ARB monotherapy to FDC treatment? (D)

d) Which observable patient characteristics (e.g., age, sex, baseline BP range, clinical conditions, BMI, etc.) are associated with initial FDC treatment (versus initial monotherapy treatment) in practice? (R)

e) How are different treatment regimes (e.g., ARB monotherapy, FDC, etc.) associated with achieving blood pressure target levels in practice, controlling for patient characteristics? (R)

3. Disease Background

The International Society of Hypertension and World Health Organization define hypertension as a sustained blood pressure (BP) of ≥140/90mmHg for most patients (but lower for diabetic patients at ≥130/80mmHg). Hypertension is graded according to blood pressure ranges. Treatment recommendations vary with grade (Table 1).

Table 1. Grades of hypertension and associated treatment recommendations

Blood pressure (BP) category	Systolic BP mm Hg	Diastolic BP mm Hg	Lifestyle intervention	Drug therapy
Normal	<120	<80	–	–
High-normal	135–139	85–89	Yes	Consider*
Mild hypertension (grade 1)	140–159	90–99	Yes	Consider†
Moderate hypertension (grade 2)	160–179	100–109	Yes	Yes
Severe hypertension (grade 3)	⩾180	⩾110	Yes	Yes

*Drug therapy may be indicated for people with established cardiovascular disease, chronic renal disease, or diabetes with complications at BP levels > 130/80 mm Hg.
†Drug therapy is recommended for people with established cardiovascular disease or diabetes or evidence of target organ damage or a 10 year cardiovascular risk ⩾ 20%.

Source: Joint British Societies (2005).

Essential (primary) hypertension is diagnosed when no identifiable cause can be found and accounts for 95% of all cases of hypertension. Secondary hypertension, where a cause can be identified, accounts for less than 5% of cases. In classic essential hypertension both the systolic and diastolic blood pressures are high, but isolated systolic and isolated diastolic hypertension are also seen. Malignant or accelerated hypertension is associated with a rapid rise in arterial pressure and, if untreated, results in rapid end-organ damage and death. The term "benign" essential hypertension has been used to describe a less aggressive form of hypertension but this term is not widely accepted because the condition is not benign. It is associated with significant morbidity and mortality. Resistant hypertension is used to describe cases of hypertension that are refractory to standard medical therapy (three different classes of anti-hypertensive drugs) (Forbes et al. 2010).

Hypertension can be broadly classified as "high renin" or "low renin". Correspondingly, there are two categories of antihypertensive drug, those which inhibit (ACE inhibitors, ARBs and beta-blockers) and those which do not inhibit (calcium channel blockers (CCBs) and diuretics) the renin-angiotensin system. Renin-profiling studies have demonstrated that younger people of <55 years and Caucasians tend to have higher renin levels relative to older people (≥55years) or the black population (of African descent). Thus, drugs which reduce BP at least in part by suppressing the renin–angiotensin system at one point or another are generally more effective as initial BP-lowering therapy in younger Caucasian patients. In contrast, CCBs and diuretics are less effective as initial BP-lowering therapy in these patients, and are better used first-line in older Caucasians or the black population of any age. ARBs remain 2nd/3rd line therapies, mainly due to the availability of cheaper alternatives such as ACE inhibitors. However this may change to 1st/2nd line when ARBs become generic (Forbes et al. 2010).

The Health Survey for England reported the prevalence of hypertension to be 3.3% in those aged under 40 years, 27.9% in those aged 40–79 years and 49.9% in those aged over 80 years. Similar figures are seen throughout the developed world, but these data probably underestimate the true prevalence of hypertension in the population owing to poor identification of cases (Forbes et al. 2010).

Hypertension contributes significantly to an individual's risk of cardiovascular disease but must be considered in the context of other cardiovascular risk factors. The risk to an individual may also correlate with the severity of the hypertension. Overall, hypertension

has been estimated to confer a 3–19% increase in the risk of stroke and a 3% increase in the risk of developing heart failure. It may account for 25% of deaths from coronary artery disease. Patients with hypertension and co-morbid diabetes, obesity or hyperlipidemia have been found to be at even higher risk for cardiovascular disease and organ damage. Hypertension is associated with marked morbidity and mortality and places a high burden on health care systems (Forbes et al. 2010).

4. Azilsartan Medoxomil

Azilsartan (TAK-491) is a highly selective, long acting angiotensin II receptor blocker (ARB) that can be used alone or in combination. The target product profile for Azilsartan monotherapy is that it will exhibit best in class attributes (superior BP lowering to olmesartan by 3-5 mmHg SBP), true 24 hour BP control with QD dosing, and safety profile comparable to other ARBs. The fixed dose combination (FDC) of Azilsartan with chlortharidone (CLD) will also exhibit best in class attributes for BP lowering, demonstrated 24-hour BP control, and safety profile comparable to other FDC's (ARB/HCT).

Azilsartan will be launched into a crowded and highly competitive antihypertensive ARB market. At Azilsartan's launch approximately 85% (volume) will be brands, but will drop to 7% 5 years later. Combination therapy (ARBs with diuretics) continues to grow. The brand vision is that Azilsartan creates additional opportunities for grade 2-3 hypertensive patients with additional risk factors to avoid life-altering events due to complications of their disease.

5. Cegedim's THIN Electronic Medical Record Database

The Health Improvement Network ('THIN') database is a computerised database of anonymised longitudinal medical records from UK primary care practices using the ViSion computer system (In Practice Systems, London, UK) to manage patient records. Currently, 479 practices participate. Data are available for a total of 9.15 million patients since 1985, including 3.36 million active cases. As of 2009, the dataset covered 5.7% of the UK population (CSD Medical Research 2011a). Data are collected on patient demographics and practice enrolment dates, diagnoses (recorded using the Read Clinical Classification version 2), referrals to secondary care (including hospital admissions and discharge diagnoses/medication data), prescriptions (recorded using the Multiflex coding system), anonymised free text, and postcode-level geographic information on socioeconomic, ethnicity and environmental variables (CSD Medical Research 2011b). Some laboratory results and measurements taken during patient visits are also recorded in THIN (Lewis et al. 2007).

THIN is a relatively young database. However, there is some historical overlap in practice sites with the well-validated GPRD database. Lewis et al. (2007) tested the strength of several well-known clinical associations in the THIN database and compared results from GPRD practices with those in non-GPRD practices. They concluded that data were equally valid in the two subsets. At least one study has attempted to externally validate data reported by primary care practices participating in the THIN data collection scheme.

Maguire, Blak and Thompson (2009) studied the reliability and timeliness of mortality reporting and developed a THIN practice-level data quality initiative. The Acceptable Mortality Reporting (AMR) indicator gives the year from which the practice is determined to reliably report all-cause mortality. Bourke, Dattani and Robinson (2004) evaluated the potential suitability of the THIN database for medical and pharmaceutical research. They concluded that data quality is assessable and that by implementing strong quality assurance procedures, THIN database records should be highly suitable for research. Since then, several studies have verified the utility of the THIN database for research on particular diseases.

The THIN database has been used in a high profile study of quality of care for patients with hypertension (Serumaga et al. 2011). MacDonald and Morant (2008) compared prevalence and treatment of clinically documented hypertension in the THIN database with that reported based on BP readings taken during a single visit as part of the Health Survey for England (HSE) in 1998 and 2003. They found lower prevalence in THIN database subjects than in the HSE. This may be partly explained by under-diagnosis and treatment of hypertension in the population.

Of particular relevance to the present proposed study, Harrison, Lancashire and Marshall (2008) investigated terminal digit bias in blood pressure readings (that is, the tendency to round the final digit of systolic and/or diastolic blood pressure readings to a round number, potentially leading to misclassification of hypertension severity) using the THIN database. They found that the extent of the problem fell dramatically over the 10 year study period from the mid-90s to mid-2000s. However, some practices continued to underestimate hypertension prevalence owing to their tendency to round the final digit of the systolic BP reading to zero.

Although demographically representative of the UK population, comparison of patients in the THIN database and the QResearch network, another UK primary care database, suggested that patients in THIN practices were more likely to be affluent (Cox et al. 2008). As socioeconomic status has been associated with health outcomes, to the extent that the THIN database is under-representative of socioeconomically deprived members of the UK general population, some findings based on THIN data should be interpreted with caution.

Approval of the THIN Scheme was granted by the NHS South-East Multi-centre Research Ethics Committee (MREC) in 2002. Studies which use only retrospective, anonymised data do not require additional MREC review. However, such studies must apply to CSD Medical Research's Scientific Review Committee for scientific approval (CSD Medical Research 2011c).

6. Study Design

Retrospective, cross-sectional, medical record database study.

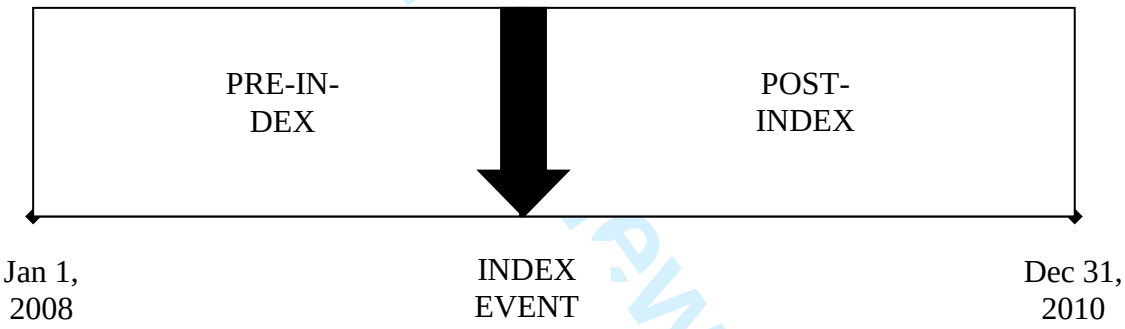
7. Study Period

Medical record data will be obtained for a three year period covering calendar years (CYs) 2008-2010. Patients will be required to be continuously registered at a practice included in the data for a minimum of 19 months during this 36 month period.

A pre-index period of a minimum of 13 months starting in January 2008 during which patients are not treated for hypertension will be sufficient to establish a 'clean' or 'treatment naive' period prior to the index event of a newly treated case of hypertension. The index date will be the date of the first prescription for an antihypertensive medication following at least 13 months free from such medication at the outset of the study period. Patients will be followed for a minimum period of 6 months post-index treatment initiation to allow time to observe the effects of treatment on hypertension outcomes (figure 2).

The use of the minimum practical study duration is recommended so as to reduce the loss of patients who are registered at practices included in the dataset for relatively short periods and may enhance the representativeness of the study population.

Figure 2. Study timeline



8. Study Population

The study population includes adults (ages 18 and older) with newly diagnosed (i.e., treatment naive) primary (essential) hypertension as identified by a Read diagnosis code in the electronic medical record (EMR) indicating essential hypertension. Patients with gestational hypertension and secondary hypertension are to be excluded.

To identify treatment naive patients, we will first select patients who were alive and permanently registered at a THIN database practice site during the study period. Patients may or may not have a diagnosis code indicating essential hypertension during the 13 month pre-index period. However, they must not have had a prescription for an antihypertensive medication during that period.

Since antihypertensive medications may be prescribed for indications other than essential hypertension, patients will be included only if they had a diagnosis indicating essential hypertension at some point during the study period and no diagnosis consistent with secondary or gestational hypertension during the same period.

Studies have shown that healthcare claims data accurately capture most patients with hypertension using diagnosis codes (Sennett 2000). The same finding would be expected with diagnoses coded in electronic medical records. This method is suggested over use of actual blood pressure readings to define hypertension since it better allows for exclusion of secondary and gestational hypertension as well as hypertensive emergencies and other causes of high blood pressure not associated with primary hypertension. However, provided that sufficient data on blood pressure readings are available in the dataset, we will confirm the diagnosis of hypertension by examining blood pressure readings from the pre-index period.

Inclusion criteria. Patients will be included if all of the following criteria are met:

- The patient is at least 18 years old at the start of the study period.
- A minimum of 19 months of continuous coverage (during a three calendar year period) in the THIN database.
- A diagnosis of essential (primary) hypertension at any point during the study period.
- A prescription for at least one antihypertensive drug (the index event) at some point after the end of the first 13 months of data and before the start of the final 6 months of data available for the patient.
- At least one blood pressure reading during the pre-index period.
- At least one blood pressure reading during the post-index period.

Exclusion criteria. Patients will be excluded if any of the following criteria are met:

- A prescription for one or more antihypertensive drugs during the 13 month pre-index period.
- A diagnosis of secondary or gestational hypertension at any time during the study period.

Sample size. TBD

9. Exposures, Outcomes, and Covariates

Exposures: Antihypertensive Pharmaceuticals

Hypertension guidelines recognize five primary drug classes: thiazide/thiazide-like diuretics, beta blockers (BBs), calcium channel blockers (CCBs), ACE inhibitors (ACEIs), and ARBs [i.e., candesartan (atacand), eprosartan (teveten), irbesartan (avapro), telmisartan (micardis), valsartan (diovan), losartan (cozaar), and olmesartan (benicar)].

This study will examine the use of the five primary classes of anti-hypertensive medications, as monotherapy or in fixed dose combinations, as well as other anti-hypertensive drugs used in general practice.

Relevant drugs will be identified using codes from Chapter 2 of the British National Formulary (BNF) as follows: thiazides and related diuretics (2.2.1), loop diuretics (2.2.2), potassium sparing diuretics (2.2.3), potassium sparing diuretics with other diuretics (2.2.4), beta-adrenoceptor blocking drugs (2.4), vasodilator antihypertensive drugs (2.5.1), centrally acting antihypertensive drugs (2.5.2), adrenergic neuron-inhibiting drugs (2.5.3), alpha-adrenoceptor-blocking drugs (2.5.4), drugs affecting the renin–angiotensin system (2.5.5), including ACE inhibitors (2.5.5.1) and angiotensin-II receptor antagonists (ARBs) (2.5.5.2), renin inhibitors (2.5.5.3), and calcium channel blockers (2.6.2).

Outcomes

Identification of FDC and monotherapy patient populations. A primary purpose of this study is to classify patients according to whether or not they would benefit from initial FDC therapy, whether or not they would benefit from remaining on ARB monotherapy for as long as possible, or neither of the above treatment protocols.

A survey of guidelines and other literature on appropriate drugs and combinations will be conducted to determine the most widely accepted treatment recommendations for sub-groups of patients with particular risk factors and comorbid conditions. Patients will be categorized accordingly in preparation for analyses.

Blood pressure control. Another outcome of interest is blood pressure control during the post-index period. Systolic and diastolic blood pressure readings will be obtained from the EMR for the period following index initiation of treatment for hypertension.

High blood pressure will be defined as readings ≥140/90 mmHg in general, and ≥130/80 mmHg for patients identified as "high risk," based upon presence of comorbid diabetes mellitus, chronic kidney disease, carotid artery disease, peripheral arterial disease, or abdominal aortic aneurysm (Rosendorff, Black, Cannon, et al, 2007).

Target blood pressure will be defined as ≥90/60 mmHg (National Heart Lung and Blood Institute, 2011) but less than the value for high blood pressure.

Patients will be identified as having high blood pressure if the most recently available measurement is in the "high" range and will be identified as being at target blood pressure if the most recently available measurement is in the target range.

Blood pressure readings will be further categorised into hypertension grade following the thresholds shown in Table 1.

Covariates

Independent Variables can be grouped into five major classes and will be constructed based upon the index date (patient demographics, socioeconomic status), pre-index period (lifestyle characteristics, illness burden, chronic/comorbid conditions), or post-index period (antihypertensive medications).

i. Patient demographics, including age, sex, and region of residence;

ii. Patient lifestyle variables, including tobacco use/smoking status, alcohol misuse, and body mass index.

iii. Socioeconomic status, as proxied by Townsend Deprivation Score (available at the patient postal code level in THIN), a composite score based on census data on assets and employment in the enumeration district or ward (Adams, Ryan and White 2005);

iv. Overall health status/illness burden as proxied by the Charlson Comorbidity Index (Deyo, Cherkin, and Ciol 1992) and following Khan et al. (2010) to map the relevant diagnosis codes from ICD-9 to Read codes;

v. Chronic conditions, including diabetes mellitus, chronic kidney disease, carotid artery disease, peripheral arterial disease, abdominal aortic aneurysm, hyperlipidemia, stroke, ischemic heart disease, and congestive heart failure; and

vi. Hypertensive medications prescribed, including ace inhibitors, ARBs, beta-blockers, calcium channel blockers, thiazide/thiazide-like diuretics, other antihypertensive drugs, and combination therapies.

10. Statistical Analysis

The proposed methods comprise a mix of descriptive analyses and logistic regression analyses.

1. Guideline review: Conduct a review of UK/European and other relevant guidelines and summarize key recommendations with particular emphasis on recommendations pertaining to initial treatment with FDC therapy and contraindications to FDC therapy. This will provide information on current clinical best practices in the treatment of newly diagnosed hypertension and identify exceptions to standard recommendations based on clinical findings and other important patient characteristics.

2. Descriptive analysis: To better understand the potential market for Azilsartan Medoxomil in fixed dose combination versus ARB monotherapy, determine the percentage of newly diagnosed patients that are indicated for initial FDC treatment and the percentage of patients who would benefit from sustained ARB monotherapy.

    a. Use the THIN medical record database to identify the number of newly diagnosed/treated patients with risk factors indicating the potential need for initiation with fixed dose combination therapy according to clinical guidelines. Identify patients with markedly elevated BP and those who are at high or very high risk of cardiovascular complications.

        i. Compute the percentage of such patients from among all patients eligible for ARB therapy owing to elevated BP and cardiovascular risk.

        ii. Compute the percentage of patients in this FDC risk group who are treated initially with FDC (versus monotheraphy) and compare this to the percentage of patients who are not in the FDC risk group who are treated initially with FDC (versus monotherapy).

    b. Use the THIN medical record database to identify the number of newly diagnosed/treated patients with risk factors indicating that FDC therapy would not be optimal (e.g., patients with, or at risk of developing, diabetes).

        i. Compute the percentage of patients who are indentified as being poor candidates for FDCs from among all patients eligible for ARB therapy owing to elevated BP and cardiovascular risk.

        ii. Compute the percentage of patients in this risk group who are treated initially with monotherapy (versus FDC) and compare this to the percentage of patients not in this risk group who are treated with monotherapy (versus FDC).

    c. Compute the percentage of patients who try multiple ARBs prior to switching to FDCs and the percentage who switch directly from an ARB to an FDC during the study period. Compute mean time-to-switch between groups of patients who switch between ARBs versus switching from an ARB directly to an FDC.

3. Multivariate analysis: To better understand which patient characteristics are predictive of initial FDC therapy versus sustained monotherapy,

    a. Prior to conducting multivariate adjusted analyses, descriptive statistics of all independent and dependent variables will be provided. Differences in means will be examined using t-statistics and differences in categorical variables will be examined using chi-square statistics.

b. Logistic regression analysis will be used to examine which patient characteristics (e.g., age, sex, baseline BP range, clinical conditions, BMI, etc.) are associated with initial FDC treatment (versus initial monotherapy treatment) in practice.

c. Logistic regression analysis will be used to estimate the relationship between different treatment regimes and BP goal outcomes, controlling for patient characteristics and time from diagnosis to most recent BP reading. If sufficient data exist, separate models will be estimated for patients who are expected to benefit from initial FDC therapy and those who may be advised to avoid FDC therapy.

11. Limitations of the Study Design, Data Sources, and Analytic Methods

In addition to the usual limitations of retrospective analyses based on medical records that were collected for administrative purposes rather than for research, there are several potential pitfalls of the proposed analyses. These may limit the ability of phmr to undertake the analyses as specified above and/or may limit the robustness and generalisability of findings. Although we will endeavour to obtain information on the data limitations prior to data acquisition, some issues may not become fully apparent until data have been acquired and data processing begins.

Potential pitfalls include the following:

- Cell sizes may be limited owing to relatively small numbers of newly diagnosed patients with high risk characteristics in the data.
- Lack of complete data from inpatient and other encounter types may limit our ability to identify high risk patients.
- Missing data on BMI and lifestyle factors may limit the regression analyses.
- Insufficient data on blood pressure readings prior to diagnosis and later in the study period may limit analysis on the relationship between treatment regimen and success in meeting blood pressure goals.
- Given that most patients with primary hypertension are ages 40 and older, it is likely that a relatively small portion of the study population will be ages 18-39, and individuals in this cohort will be unrepresentative of the market as a whole. Consequently, it may be sensible to limit analyses to middle age and older adults.

12. Plans for Disseminating and Communication Study Results

The investigators and sponsors are committed to wide dissemination of the study findings. The study plan approved by the sponsors includes a timeline for submitting abstracts to major European and international cardiovascular and hypertension society meetings. This plan also includes a provision for one or more manuscripts to be prepared and submitted for peer-reviewed academic publication. The STROBE guidelines for reporting observational studies will be followed (von Elm et al. 2007).

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **[See the title, page 1, and 'design' section of the abstract, page 2]**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **[See 'primary and secondary outcome measures' and 'results' sections of abstract, page 2]**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **[pages 4-5]**
Objectives	3	State specific objectives, including any prespecified hypotheses **[final paragraph of the 'introduction' section, page 5]**
Methods		
Study design	4	Present key elements of study design early in the paper **[pages 5-9]**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **[page 5]**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **[pages 6-7]**
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed **[n/a]**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **[pages 7-8]**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **[pages 7-8]**
Bias	9	Describe any efforts to address potential sources of bias **[See page 8 with more information included in the 'study limitations' section, page 22]**
Study size	10	Explain how the study size was arrived at **[See page 6 and 'study population' under 'results', page 9]**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **[page 9]**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **[page 9]**
		(*b*) Describe any methods used to examine subgroups and interactions **[pages 8-9]**
		(*c*) Explain how missing data were addressed **[page 9]**
		(*d*) If applicable, explain how loss to follow-up was addressed **[n/a, the study inclusion criteria stipulated that all patients were required to have 6 months follow up in the data]**
		(*e*) Describe any sensitivity analyses **[n/a]**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **[page 10]**
		(b) Give reasons for non-participation at each stage **[n/a]**
		(c) Consider use of a flow diagram **[n/a]**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **[page 10 and table 1]**

		(b) Indicate number of participants with missing data for each variable of interest **[Table 4]**
		(c) Summarise follow-up time (eg, average and total amount) **[n/a, study restricted to 6 month follow up period available for all participants]**
Outcome data	15*	Report numbers of outcome events or summary measures over time **[Tables 2 and 4]**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **[Tables 3 and 5]**
		(*b*) Report category boundaries when continuous variables were categorized **[Tables 3-5]**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **[n/a]**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **[n/a]**
Discussion		
Key results	18	Summarise key results with reference to study objectives **[Page 19]**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **[Page 22]**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **[Pages 19-21]**
Generalisability	21	Discuss the generalisability (external validity) of the study results **[Page 22]**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **[See 'funding' and 'competing interests' data uploaded with submission]**

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Relationship between initial therapy and blood pressure control for high-risk hypertension patients in the United Kingdom: a retrospective cohort study from the THIN General Practice Database

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Keywords:	Hypertension < CARDIOLOGY, Combination therapy, NICE Clinical Guidelines, The Health Improvement Network (THIN), High-risk patients

Relationship between initial therapy and blood pressure control for high-risk hypertension patients in the United Kingdom: a retrospective cohort study from the THIN General Practice Database

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Keywords

Hypertension, combination therapy, diabetes mellitus, kidney disease, cardiovascular disease, The Health Improvement Network (THIN) database, NICE clinical guidelines.

Abstract

Objective: To examine UK practice patterns in treating newly diagnosed hypertension and to determine whether subgroups of high-risk patients are more or less likely to follow particular therapeutic protocols and to reach blood pressure goals.

Design: Retrospective cohort study.

Setting: This study examined adults in The Health Improvement Network (THIN) UK general practice medical records database who were initiated on medication for hypertension.

Participants: 48,131 patients with essential hypertension diagnosed between 2008-2010 who were registered with a participating practice for a minimum of 13 months prior to, and 6 months following, initiation of therapy. We excluded patients with gestational hypertension or secondary hypertension. Patients were classified into risk groups based on blood pressure readings and comorbid conditions.

Primary and secondary outcome measures: Odds of receiving single vs. fixed- or free-drug combination therapy and odds of achieving blood pressure control were assessed using multivariable logistic regression.

Results: The vast majority of patients (95.8%) were initiated on single drug therapy. Patients with high cardiovascular risk (patients with grade 2-3 hypertension or those with high normal/grade 1 hypertension plus at least one cardiovascular condition pre-treatment) had a statistically significant benefit of starting immediately on combination therapy when blood pressure control was the desired goal (OR: 1.23; 95% CI: 1.06–1.42) but, surprisingly, were less likely than patients with no risk factors to receive combination therapy (OR, adjusted: 0.53; 95% CI: 0.47–0.59).

Conclusions: Our results suggest that combination therapy may be indicated for patients with high cardiovascular risk, who accounted for 60.6% of our study population. The NICE guideline CG34 of 2006 (in effect during the study period) recommended starting with single drug class therapy for most patients, and this advice does seem to have been followed even in cases where a more aggressive approach might have been considered.

Strengths and limitations of this study

- This is one of the largest nationally representative studies of hypertension practice and outcomes in the UK.
- We had access to a very large general practice dataset to identify patient risk factors, but without data on inpatient encounters, the proportion of high-risk patients may have been underestimated.
- The dataset benefited from near complete reporting of follow up blood pressure readings after therapy initiation, but the 6 month follow up period precluded analysis of long term blood pressure control outcomes.
- It may be beneficial to extend this analysis using data from 2012 onwards to assess the impact of the updated 2011 NICE guidelines upon choice of therapeutic agents amongst particular subgroups of the population and whether these choices affected outcomes in clinical practice.

INTRODUCTION

Hypertension—generally defined by sustained blood pressure (BP) ≥140/90mm Hg—is one of the most common premorbid conditions contributing to deadly disease in the United Kingdom. The Health Survey for England reported the prevalence of hypertension to be 27.9% in those aged 40–79 years rising to 49.9% in those aged over 80 years. A similarly high prevalence of hypertension is seen in adults in nearly every country throughout the developed world.[1,2]

More than 7% of deaths worldwide are directly attributable to hypertension, exceeding rates for tobacco use and high cholesterol.[3] Hypertension has been estimated to confer a 3–19% increase in the risk of stroke and a 3% increase in the risk of developing heart failure. It may account for 25% of deaths from coronary artery disease.[2] Patients with hypertension and co-morbid diabetes, obesity or hyperlipidemia have been found to be at even higher risk for cardiovascular disease and end-organ damage.[4] Hypertension places an extraordinarily high economic burden on health care systems through the developed world.[2,5]

At the same time, hypertension is one of the most significant, single, modifiable risk factors associated with cardiovascular disease and stroke, and appropriate treatment has been shown to significantly reduce both morbidity and mortality associated with these conditions.[2,6,7] Together with diet and lifestyle modifications, a range of pharmaceutical therapies have been found to be highly effective in controlling hypertension.[8]

Recommended initial therapy for patients with hypertension varies from country to country. In the United Kingdom, physicians are advised to start patients on

monotherapy and add an additional drug only in the case of failure to reach blood pressure goal on an adequate dose of a single drug.[9,10] European guidelines have for more than a decade emphasized the importance of considering additional cooccurring cardiovascular, renal and metabolic conditions when initiating treatment for hypertension, recommending different strategies depending upon overall cardiovascular risk.[11]

The purpose of this study is to examine real world practice in the treatment of newly diagnosed hypertension in the UK, comparing treatment pathways for low and high risk individuals. Our aim is to determine whether particular subgroups of patients (e.g., those with diabetes, renal disease, or additional cardiovascular risk factors) are more or less likely than others to follow particular therapeutic protocols and to meet immediate blood pressure goals following therapy initiation.

METHODS

To investigate initial therapy for new onset hypertension in the United Kingdom, we acquired patient-level data from The Health Improvement Network ('THIN') over a three year period, from 2008-2010, utilizing a computerised database of anonymised longitudinal medical records covering approximately 500 UK primary care practices.

The THIN database covers 5.7% of the UK population[12] and captures patient demographics and practice enrolment dates, diagnoses, referrals to secondary care, prescriptions, laboratory results and measurements taken during patient visits.[13,14] These data have been used to study patients with hypertension in the past.[15-17]

Approval of the THIN Scheme was granted by the NHS South-East Multi-centre Research Ethics Committee (MREC) in 2002.[18] Per requirements of the MREC, the present study was granted scientific approval by the data vendor's Scientific Review Committee in March 2012. The study protocol is available as a web supplement to this article. This manuscript was prepared in compliance with the STROBE guidelines for cohort studies.[19]

Study design

We conducted a retrospective cohort study of adults newly treated for hypertension during calendar years 2008-2010. Patients were required to be continuously registered at a practice for a minimum of 19 months during this period.

The study population included adults (ages 18 and older) with newly treated primary (essential) hypertension as identified by a Read diagnosis code in the electronic medical record (EMR) indicating essential hypertension. Patients with gestational hypertension and secondary hypertension were excluded.

We used diagnosis codes, rather than use of actual blood pressure readings, to define hypertension since that approach better allows for exclusion of secondary and gestational hypertension as well as hypertensive emergencies and other causes of high blood pressure not associated with primary hypertension.

To identify newly treated hypertension, we imposed a pre-index 'clean' period of a minimum of 13 months during which patients did not receive a prescription for an antihypertensive medication. This period was chosen since well-controlled patients with hypertension may be expected to visit their general practitioner (GP) at least

annually for follow up. We allowed an extra month in case of delay in scheduling an annual appointment to obtain a prescription renewal.

The index date was the date of the first prescription for an antihypertensive medication following at least 13 months free from such medication at the outset of the study period.

Patients were followed for a period of 6 months after index treatment initiation (post-treatment period) to allow time to observe the effects of treatment on hypertension outcomes.

Exposures, outcomes and covariates

Antihypertensive therapy. Hypertension guidelines recognize five primary drug classes: thiazide/thiazide-like diuretics, beta blockers (BBs), calcium channel blockers (CCBs), ACE inhibitors (ACEIs), and angiotensin receptor blockers (ARBs). This study examined the use of the five primary classes of anti-hypertensive medications, as monotherapy or in combination, as well as other anti-hypertensive drugs used in general practice. Relevant drugs were identified using codes from Chapter 2 of the British National Formulary (BNF).

Blood pressure control outcomes. Systolic and diastolic blood pressure readings were obtained from the EMR. The last recorded measurement during the periods immediately prior to treatment initiation (pre-treatment period) and in the six months following treatment initiation (post-treatment period) were used to categorize patients into hypertension grade, pre- and post-index. A patient was classified into the

highest grade appropriate based on either their systolic or diastolic reading. Blood pressure was defined as 'in control' or 'out of control' in the post-treatment period depending upon blood pressure readings in relation to the threshold target recommended by NICE of 140/90 .

Covariates. Independent variables were constructed based upon the index date (patient demographics and socioeconomic status) or pre-index period (lifestyle characteristics and chronic/comorbid conditions).

i. Patient demographics: age (in years) and sex;

ii. Patient lifestyle variables (measured using Read codes recorded during the pre-index study period): tobacco use (defined as current smoker) and overweight/obese status (measured as BMI>=30 or Read code indicating overweight/obese); and

iii. Chronic conditions (measured using Read codes for all diagnoses on record up to the index treatment date): diabetes mellitus, renal disease, coronary heart disease (not including myocardial infarction), cerebrovascular disease, peripheral vascular disease, myocardial infarction or hyperlipidemia.

Risk cohorts

Patients were assigned to risk groups based on a combination of their pre-treatment blood pressure grade and the presence of comorbid conditions following criteria outlined by Mancia and colleagues (2013) in their guidelines for management of hypertension.[11] A patient was considered 'high risk' on the basis of potential

cardiovascular morbidity if he or she had a pre-treatment hypertension grade of 2 or 3 or if blood pressure was in the high-normal to mild range in the presence of one or more key cardiovascular conditions (i.e., coronary heart disease, cerebrovascular disease, peripheral vascular disease, myocardial infarction or hyperlipidemia). Patients with kidney disease (with or without diabetes) and those with diabetes (without coexisting kidney disease) were also considered 'high risk'. All others were classified as 'low risk'.

Missing data

UK medical records typically provide nearly complete data for the key study variables identified here. The UK "Quality and Outcomes Framework",[20] introduced in 2004, provides financial incentives for UK general practitioners to appropriately document important metrics and meet selected quality process and outcome goals. Physicians are paid incentive bonuses for keeping a registry of patients with hypertension being treated in their practice and for recording blood pressure in hypertensive patients every 9 months, at a minimum. For patients with diabetes or kidney disease, additional incentives are offered to regularly monitor blood pressure regardless of whether hypertension has been diagnosed. Incentives are also provided for keeping a registry of patients with BMI>=30 in the prior 15 months and for recording smoking status among patient with hypertension or other cardiovascular or metabolic conditions.

For the purposes of analyses, continuous variables (such as BMI) were recoded into categories. Where data were missing, the patient was assumed to fall into the

reference category. The exception was blood pressure recordings, where we created a separate category for missing data.

Statistical analysis

We employed a mix of descriptive analyses and logistic regression analyses using SAS software, Version 9.3 for Windows.

Simple descriptive statistics were included to illustrate characteristics of the population, initial treatment regimen, prescription switches in the 6 month post-treatment initiation period, and blood pressure control status in the 13 month pre-treatment period and in the 6 month post-treatment period.

Logistic regression models were used to examine the association between patient characteristics and outcomes of interest. Risk groups were identified in the models and separate models were run for each risk group to examine interactions. Analyses were restricted to patients who had follow-up blood pressure recorded as this was necessary to evaluate the outcome of blood pressure control. All models were subjected to the Hosmer-Lemeshow goodness of-fit test. Since this test may be sensitive to sample size,[21] we also calculated the c-statistic. Effects are expressed as odds ratios (ORs). Statistical significance of independent variables in each model was evaluated at the alpha<0.05 level. Bonferroni correction was used to maintain this familywise error rate in the presence of multiple pair-wise comparisons.

A sensitivity analysis was performed to assess the potential impact of missing data on blood pressure readings. The blood pressure control regression analysis was re-run twice for each risk group and for all patients: under the first scenario, we

assumed that all patients with missing blood pressure readings had achieved blood pressure control following treatment; under the second scenario, we assumed that they had not.

RESULTS

Study population

A total of 48,131 patients were found to meet all study criteria. Just over half of the population was male with a mean age of 57.3 years. **Table 1** summarizes demographic and key lifestyle variables by risk group. One-third of patients had been diagnosed with one or more risk-elevating comorbid conditions (diabetes, renal disease and cardiovascular disease) prior to index treatment initiation. Others were classified as high risk based on pre-treatment blood pressure readings indicating grade 2 or 3 hypertension. We found high rates of overweight/obesity and smoking across groups.

Index antihypertensive therapy

The vast majority of patients (95.8%) were initiated on single drug therapy. **Table 2** shows the distribution of patients by index treatment pathway and risk cohort. Combination therapy (either fixed dose combination drugs or multiple single agents prescribed on the index date) was highest for patients with renal disease, at 6.0%, and lowest for patients in the cardiovascular risk group (grade 2 or 3 hypertension pre-treatment or those with high-normal or grade 1 hypertension in combination with one or more cardiovascular conditions). The most common drug class used in monotherapy, across all risk classes, was ACE-inhibitors, followed by calcium channel blockers.

Table 1. Age and sex distribution of the study population (%)

	High Risk Patients			Low Risk Patients	All Patients
	Kidney Disease	Diabetes Mellitus	Cardio-vascular*		
Age, years					
Mean	67.0	56.8	57.1	55.6	57.3
Median	69.0	57.0	57.0	56.0	57.0
Male, percent	42.0%	58.2%	50.9%	50.5%	50.9%
Obese/overweight, percent	61.4%	83.8%	66.4%	65.7%	67.5%
Current tobacco use, percent	20.3%	25.8%	25.1%	23.7%	24.5%
Number of patients	3,060	4,303	29,175	11,593	48,131
% of patients	6.4	8.9	60.6	24.1	100.0

Note (*): The cardiovascular risk group includes patients with grades 2 or 3 hypertension (with or without comorbid cardiovascular disease) prior to treatment initiation and those with 'high normal' or grade 1 hypertension plus one or more cardiovascular conditions (i.e., coronary heart disease, cerebrovascular disease, peripheral vascular disease, myocardial infarction or hyperlipidemia).

Table 2. Monotherapy versus fixed- or free-drug combination therapy, by risk cohort, n= 48,131 (%)

Antihypertensive Drug Class	Kidney Disease	Diabetes Mellitus	High Risk Cardio-vascular*	Low Risk Patients	All Patients
Combination therapy	6.0	4.0	3.2	6.3	4.2
Monotherapy					
ACE-Inhibitors	40.3	61.5	43.0	36.6	42.3
ARBs	3.4	3.5	2.2	2.5	2.4
Calcium channel blockers	25.4	16.7	30.8	22.6	27.7
Diuretics	17.2	9.1	15.4	17.8	15.7
Beta Blockers	4.9	3.3	4.4	10.3	5.9
Other antihypertensive drugs	2.8	1.8	1.1	3.9	1.9

Note: Columns may not sum to 100% because of rounding.

Table 3 shows the results of a multivariate logistic regression of the odds of receiving combination therapy as a function of patient characteristics, including risk cohort. The first model included only patient characteristics (other than risk group), the second included risk groups alone, unadjusted for other patient characteristics, and the third model included risk groups adjusted for patient characteristics (excluding pre-treatment hypertension grade which was included in the definition of the cardiovascular risk group). In model 3, we excluded comorbid conditions since the presence of one or more of these conditions is an integral part of the definition of the high risk groups that were included in this model.

Table 3. Odds of receiving fixed- or free-drug combination therapy versus monotherapy as index treatment

Variable	Model 1: Patient Variables only Odds Ratio [95% CI]	Model 2: Risk groups only Odds Ratio [95% CI]	Model 3: Adjusted Odds Ratio [95% CI]
Age cohort			
Age<55			
Age >=55	0.946 [0.848, 1.055]		1.114 [1.004, 1.236]
Sex			
Female			
Male	**1.385 [1.248, 1.537]**		**1.552 [1.404, 1.716]**
Registration with practice			
Existing patient			
New patient	**1.661 [1.301, 2.120]**		**1.715 [1.353, 2.174]**
History of hypertension			
No prior hypertension			
Prior episode of hypertension	**1.756 [1.580, 1.952]**		**2.144 [1.938, 2.371]**
Lifestyle factors			
Not current smoker			
Current smoker	**1.245 [1.113, 1.394]**		**1.269 [1.138, 1.415]**
Not obese/overweight			
Overweight	0.972 [0.858, 1.102]		0.904 [0.801, 1.020]
Obese	1.073 [0.945, 1.218]		0.956 [0.846, 1.081]
Comorbid conditions			
Diabetes	0.812 [0.680, 0.971]		
Kidney disease	1.123 [0.932, 1.353]		
Coronary heart disease	**2.980 [2.207, 4.024]**		
Cerebrovascular disease	**1.692 [1.397, 2.050]**		
Peripheral vascular disease	0.976 [0.749, 1.270]		
Myocardial infarction	**5.252 [4.498, 6.133]**		
Hyperlipidaemia	0.916 [0.799, 1.050]		
Pre-treatment hypertenion grade			
Lower than grade 1			
Grade 1	**0.272 [0.230, 0.322]**		
Grade 2	**0.185 [0.157, 0.218]**		
Grade 3	**0.352 [0.299, 0.415]**		

No pre-treatment BP reading	0.857 [0.693, 1.060]		
Risk group			
Diabetes mellitus		**0.639 [0.530, 0.771]**	**0.597 [0.494, 0.721]**
Kidney disease		1.035 [0.864, 1.240]	0.912 [0.758, 1.098]
Cardiovascular		**0.524 [0.469, 0.584]**	**0.527 [0.472, 0.588]**
Low risk			
Number of observations	44,011	44,011	44,011
Hosmer-Lemeshow Goodness-of-Fit	Pass	Pass	Pass
c-statistic	0.74	0.58	0.65

Note: Bold text indicates statistical significance at the alpha=0.05 level on a two-tailed test estimated with stepdown Bonferroni correction of p-values.

Model 1 shows that men, patients who registered with the practice during the study period, those who had an episode of hypertension prior to the study period, and current smokers all had higher odds of receiving initial treatment with combination therapy. Odds of receiving combination therapy were lower, other things equal, among those with higher grade hypertension in the immediate pre-treatment period. However, the association was non-linear. Patients with grade 2 hypertension had the lowest odds of receiving combination therapy. Patients who did not have a blood pressure reading recorded for the pre-treatment period (3.7% of all patients) were not significantly less likely to receive combination therapy than those who did.

Model 2 shows that patients with diabetes (OR, adjusted: 0.64; 95% CI: 0.53–0.77) and cardiovascular disease (OR, adjusted: 0.52; 95% CI: 0.47–0.58) were both less likely than those with no risk factors to receive combination therapy. Adjusting for demographics and lifestyle factors in Model 3 did not alter our findings.

Blood pressure control

More than two-thirds of patients (66.8%) had grade 2 hypertension or higher prior to treatment, falling to 13.5% in the post-index period. Low risk patients were, by definition, those who had no worse than grade 1 hypertension prior to treatment and without risk-elevating comorbid conditions (diabetes, renal disease and cardiovascular disease). A shift from grade 2 or 3 hypertension towards grade 1 (or lower) was observed in the follow-up period in all other subjects, including those with cardiovascular conditions (96.4% were classified in grades 2 or 3 pre-treatment vs. 16.3% afterward), diabetes (53.3% vs. 11.5%) and kidney disease (56.1% vs. 10.9%). Among low risk patients, results were somewhat less dramatic but generally positive, with 70.2% classified with grade 1 hypertension before treatment versus 42.5% with grade 1 or higher afterward (Figure 1). Overall, the proportion of patients who had blood pressure readings at or below the 'high normal' range increased more than six-fold following treatment initiation, from 5.8% to 37.4%.

To better understand factors affecting treatment success, we modeled the likelihood of achieving blood pressure control following treatment initiation as a function of therapeutic regimen (monotherapy versus combination therapy) controlling for demographics, comorbid conditions and lifestyle variables for all patients plus model variants run separately for low risk and high risk cohorts (**Table 4**). Being older significantly decreases the odds of achieving blood pressure goal for all patients except those with kidney disease or diabetes. Men with high cardiovascular risk are less likely than women in this group to achieve blood pressure control. Having ever had a prior episode of hypertension treated in the past significantly reduced the

odds of achieving control across all patient groups except those with kidney disease. Patients with diabetes (OR: 1.16; 95% CI: 1.09–1.24) and kidney disease (OR: 1.18; 95% CI: 1.09–1.28) were each slightly more likely to achieve blood pressure control than other patients.

Current smokers with cardiovascular health conditions were less likely to reach blood pressure target (OR: 0.87; 95% CI: 0.82–0.92). Obesity reduced the odds of achieving goal for both cardiovascular risk patients (OR: 0.87; 95% CI: 0.82–0.93) and those deemed low risk (OR: 0.86; 95% CI: 0.77–0.95). However, being merely overweight was associated with slightly higher odds of reaching goal among those in the cardiovascular high risk group (OR: 1.11; 95% CI: 1.05–1.18).

Across all patients and risk sub-groups, the odds of achieving blood pressure control fell with increasing hypertension grade. For the full sample of patients, we found that starting on combination therapy increased the odds of achieving blood pressure control relative to starting with mono-therapy.

We performed a sensitivity analysis to assess the potential impact of missing data on blood pressure readings by re-rerunning the analyses on all patients, first assuming that all patients with missing blood pressure readings had achieved blood pressure control following treatment and, second, assuming that they had not. There were no substantive changes in the coefficients under either scenario, though a few of the covariates (prior hypertension, current smoking status, and overweight BMI) became insignificant under the first scenario assuming that all patients with missing BP recordings had met the blood pressure control goal.

Table 4. Odds of achieving blood pressure control in the post-treatment period as a function of treatment regimen and risk factors (95% CI in parentheses)

Variable	Kidney Disease	Diabetes Mellitus	Cardiovascular*	Low Risk Patients	All Patients
Age cohort					
Age<=55					
Age >55	0.897 [0.727, 1.107]	0.854 [0.744, 0.980]	**0.770 [0.730, 0.812]**	**0.785 [0.723, 0.853]**	**0.789 [0.757, 0.822]**
Sex					
Female					
Male	1.016 [0.867, 1.191]	0.942 [0.823, 1.077]	**0.797 [0.757, 0.839]**	0.918 [0.846, 0.996]	**0.851 [0.818, 0.886]**
Registration with practice					
Existing patient					
New patient	1.103 [0.675, 1.800]	1.260 [0.898, 1.769]	1.053 [0.908, 1.221]	0.922 [0.743, 1.143]	1.032 [0.923, 1.154]
History of hypertension					
No prior hypertension					
Prior episode of hypertension	0.790 [0.673, 0.928]	**0.715 [0.617, 0.829]**	**0.878 [0.828, 0.931]**	**0.847 [0.772, 0.928]**	**0.843 [0.806, 0.882]**
Comorbid conditions					
Diabetes	1.061 [0.845, 1.331]				**1.161 [1.085, 1.242]**
Kidney disease					**1.180 [1.088, 1.280]**
Coronary heart disease	1.133 [0.685, 1.875]	0.731 [0.317, 1.686]	1.134 [0.841, 1.530]	1.605 [0.859, 3.001]	1.138 [0.909, 1.425]
Cerebrovascular disease	1.034 [0.776, 1.378]	1.318 [0.936, 1.858]	**1.254 [1.090, 1.443]**	**1.810 [1.314, 2.493]**	**1.278 [1.153, 1.416]**
Peripheral vascular disease	0.797 [0.585, 1.085]	1.097 [0.905, 1.330]	1.168 [0.987, 1.382]	0.715 [0.417, 1.226]	1.056 [0.944, 1.182]
Myocardial infarction	1.103 [0.804, 1.513]	**1.785 [1.210, 2.633]**	1.161 [0.976, 1.382]	**1.785 [1.349, 2.363]**	**1.315 [1.166, 1.482]**
Hyperlipidaemia	0.976 [0.818, 1.165]	1.081 [0.932, 1.255]	1.086 [1.012, 1.166]	1.106 [0.991, 1.233]	**1.078 [1.023, 1.136]**
Lifestyle factors					
Not current smoker					
Current smoker	1.180 [0.973, 1.431]	0.936 [0.805, 1.088]	**0.871 [0.821, 0.924]**	0.998 [0.908, 1.098]	**0.923 [0.882, 0.967]**

Not obese/overweight					
Overweight	0.976 [0.813, 1.171]	1.199 [0.981, 1.465]	**1.112 [1.046, 1.183]**	1.074 [0.974, 1.184]	**1.098 [1.046, 1.152]**
Obese	0.974 [0.796, 1.191]	0.971 [0.802, 1.177]	**0.874 [0.820, 0.930]**	**0.857 [0.774, 0.948]**	**0.881 [0.838, 0.925]**
Pre-treatment hypertension grade					
Lower than grade 1					
Grade 1	0.740 [0.547, 1.001]	**0.556 [0.426, 0.727]**	**0.516 [0.328, 0.812]**	**0.589 [0.519, 0.669]**	**0.583 [0.527, 0.644]**
Grade 2	**0.416 [0.309, 0.559]**	**0.343 [0.263, 0.448]**	**0.321 [0.206, 0.501]**		**0.374 [0.339, 0.413]**
Grade 3	**0.299 [0.216, 0.414]**	**0.184 [0.137, 0.248]**	**0.201 [0.129, 0.314]**		**0.234 [0.211, 0.259]**
No pre-treatment BP reading	0.448 [0.263, 0.765]	**0.330 [0.204, 0.532]**		**0.333 [0.283, 0.391]**	**0.340 [0.295, 0.392]**
Initial therapy					
Monotherapy					
Combination therapy	1.378 [0.981, 1.937]	1.138 [0.788, 1.644]	**1.228 [1.061, 1.421]**	1.118 [0.928, 1.348]	**1.213 [1.093, 1.346]**
Number of observations	2,732	3,892	27,438	9,949	44,011
Hosmer-Lemeshow Goodness-of-Fit	Fail	Pass	Pass	Pass	Pass
C-statistic	0.62	0.64	0.59	0.59	0.62

Note: Bold text indicates statistical significance at the alpha=0.05 level on a two-tailed test estimated with stepdown Bonferroni correction of p-values.
Note (*): The cardiovascular risk group includes patients with grades 2 or 3 hypertension (with or without comorbid cardiovascular disease) prior to treatment initiation and those with 'high normal' or grade 1 hypertension plus one or more cardiovascular conditions (i.e., coronary heart disease, cerebrovascular disease, peripheral vascular disease, myocardial infarction or hyperlipidemia).

DISCUSSION

In line with the UK guidelines, we found that the majority of patients were initiated on single drug therapy. Few were treated with combination therapy and patients with diabetes or cardiovascular disease were less likely to receive combination drug treatment than patients with no risk factors. Treatment initiation was beneficial (66.8% of patients had grade 2 or 3 hypertension pre-treatment vs. 13.5% post-treatment, overall). Patients with diabetes and kidney diseases were more likely than others to reach target blood pressure readings. In addition, starting on combination therapy increased the odds of achieving blood pressure control compared with starting on mono-therapy.

A population at risk

This study of patients with newly treated hypertension in the UK found that a majority had risk factors complicating hypertension, including comorbid cardiovascular conditions, diabetes and/or kidney disease alone or in combination with index blood pressure readings consistent with grade 2 or 3 hypertension. Many were also current smokers and/or were overweight or obese.

Conservative versus aggressive therapy for high risk patients

Our results may suggest that combination therapy is indicated for patients with grade 2 or 3 hypertension or high normal/grade 1 hypertension plus at least one cardiovascular condition. Although it is commonly thought that combination therapy is also necessary to attain blood pressure control in patients with diabetes or kidney

disease, our results showed that it was not a statistically significant predictor of reaching blood pressure goals in these subgroups. Based on our findings, 60.6% of patients in our study population might have benefited more from initiation on multiple drugs. However, given that past NICE guidelines promulgate initiation on monotherapy, it is perhaps not surprising that we found that only 4.2% of patients started on combination therapy. The patients who may benefit most (e.g., those in our cardiovascular high risk group) were actually the least likely to be prescribed combination therapy (3.2% compared with 6.3% of patients with no risk factors), either in the form of fixed dose combination pills or multi-drug class prescriptions.

Following the recently published SPRINT study (a randomized trial of intensive versus standard blood pressure control among patients with cardiovascular risk factors),[22] which was halted early owing to the finding that patients in the intensive arm (with goal systolic BP <120 mm Hg) had lower rates of major cardiac events and lower rates of all-cause mortality than patients in the standard arm, it is likely that target blood pressure readings for patients with cardiovascular risk factors will be lowered in the future. If so, more aggressive initial therapy for this risk cohort may be recommended.

New blood pressure goals and recommended therapies for patients with diabetes or kidney disease

Controlling blood pressure for subgroups of patients with diabetes and/or chronic kidney disease is particularly important as the combination of hypertension with either condition is associated with greatly increased risk of morbidity.[11] Our multivariable

analysis showed that patients with diabetes or chronic kidney disease were slightly more likely than other patients to meet the blood pressure target of <140/90. Although at the time that our data were collected UK patients with these conditions had been encouraged to aim for even lower readings, more recent data suggest that meeting the general threshold may be preferable, prompting changes in both European and UK guidelines.

It has been found that reduction of systolic blood pressure below 130 mm Hg is quite difficult to achieve for patients with diabetes,[11] and a reappraisal of European guidelines undertaken in 2009, and the most recent ESH-ESC guideline, backed off from recommendations of lower systolic BP goals for patients with diabetes and renal disease owing to a lack of clinical trial evidence of benefit from attaining the lower thresholds in these special populations.[11,23]

Recently adopted NICE guidelines specific to patients with diabetes, set target blood pressure at or below 140/90 unless there is kidney, eye or cardiovascular damage, in which case the goal is to keep blood pressure <130/80 mm Hg. Caution is urged in treating diabetic patients too aggressively since the risk of adverse side effects, such as orthostatic hypotension, associated with use of antihypertensive medications is raised in patients with autonomic neuropathy.[24] Some drug classes are not recommended owing to microvascular complications or metabolic problems. In general, ACEIs or ARBs are preferred as initial therapy,[25] and we found that together these drugs as monotherapy accounted for 65% of index treatment regimens chosen for patients with diabetes. Although patients with diabetes had the lowest percentage

use of diuretics of all risk groups, this drug class still accounted for 9.1% of initial therapy.

For patients with chronic kidney disease, blood pressure targets do not differ from other patients. However, when the albumin/creatinine ratio (ACR)≥30 mg/mmol, ACEIs or ARBs are the recommended therapy. Other treatment pathways may be selected in the presence of hypertension with ACR<30 mg/mmol.[26] We were not able to evaluate ACR levels. However, we did find that ACEs and ARBs accounted for 43.7% of index treatments offered to patients with kidney disease.

Strengths and Limitations of the Study Design and Data

This study was based on observations of a large, population-based sample of patients in real world practice conditions. Retrospective analyses based on medical records that were collected for administrative purposes rather than for research are subject to limitations inherent in the data, including potentially incomplete reporting of certain data elements. One key study limitation is that our study population was identified in part using READ codes in the primary care setting only. Some patients with primary hypertension may have been missed or misclassified if READ codes were incorrectly recorded or missing. Evidence is lacking to validate the use of READ codes (versus repeated blood pressure measurements) to identify cases of primary hypertension accurately.

Lack of complete data from inpatient and other encounter types may also have limited our ability to identify high risk patients. Given that UK GPs act as gatekeepers for specialist and non-emergency inpatient care, data are missing far less frequently

than in other health data systems in the US and Europe. Nevertheless, the prevalence of chronic conditions may be underestimated since diagnoses are not recorded at every visit. One UK study estimated that more than 25% of myocardial infarction events may be missed using primary care encounters data alone.[27] We attempted to mitigate this problem by counting all recorded diagnoses available for each patient, including conditions reported prior to the start of the study period.

It was not possible to assess medication compliance in our population, since prescription data in medical records indicate the physician's intention, but do not directly reveal any information regarding patient compliance with prescribed therapies including whether prescriptions were filled. While it was possible to observe changes in prescribed medications, complete information was not available on the reasons for adding or changing medications (i.e., owing to adverse effects or lack of effectiveness). A longer follow up period would be needed to examine the impact of changes in drug therapy (e.g., drug class, dose, fixed- or free drug combinations) on BP control. A longer follow up period would also be required to assess the long-term effect upon blood pressure outcomes of initial therapy choice.

Finally, selection bias may have been introduced in the regression analyses because of the necessity of limiting analysis of blood pressure control to patients who had a follow up blood pressure readings recorded. Missing follow up data on this key variable cannot be assumed to occur at random and may differ by risk cohort. However, the results of our sensitivity analysis suggest that the impact was minimal

Guidelines have recently been updated and it would be interesting to assess whether this has had an impact on how newly diagnosed patients with hypertension are treated. While the NICE guidelines remain conservative, favouring monotherapy initially, key updates included the recommendation to offer antihypertensive drug therapy to patients with stage 2 hypertension, regardless of age, to patients with diabetes or renal disease, and to patients with 10 year cardiovascular risk >=20%.[10] Replicating these analyses for the period 2012 onward to assess potential changes in practice patterns under the more recent NICE[10,25,26] and European[11] guidelines is warranted.

Conclusion

We report mixed findings on the adherence of physicians to best practice guidelines for special populations of high risk patients in the UK. The NICE guideline CG34 of 2006—in effect during the study period—recommended to start conservatively with single drug class therapy for most patients and this seems to have been followed even in cases where a more aggressive approach might have been considered. One issue this study raised is that most patients treated for hypertension in UK general practice are in fact high risk patients. Patients with diabetes, for whom there are benefits to deferring a move to multidrug therapy, were found to be less likely than patients with no risk factors to be treated aggressively initially. However, patients with extremely high blood pressure readings (grade 2 or 3) were also less likely than those with lower than grade 1 hypertension readings and no other risk factors to receive aggressive early therapy. The message that treatment must be tailored to the patient's individual

risk profile needs greater emphasis, and this may mean backing away from the historically conservative approach taken by NICE except in the case of patients with lower grade hypertension and no other risk factors.

Figure 1. Percentage of patients in each blood pressure control group, pre- and post-treatment initiation, by risk cohort

Note (*): The cardiovascular risk group includes patients with grades 2 or 3 hypertension (with or without comorbid cardiovascular disease) prior to treatment initiation and those with 'high normal' or grade 1 hypertension plus one or more cardiovascular conditions (i.e., coronary heart disease, cerebrovascular disease, peripheral vascular disease, myocardial infarction or hyperlipidemia).

Contributors: SW, AJ, JP, and TT contributed to the conception or design of the work. SW was involved in data acquisition and carried out data analysis and interpretation. SW, AJ, JP and TT participated in the drafting of the article. SW and TT were responsible for the critical revision of the article. SW, AJ, JP and TT gave final approval of the version to be published.

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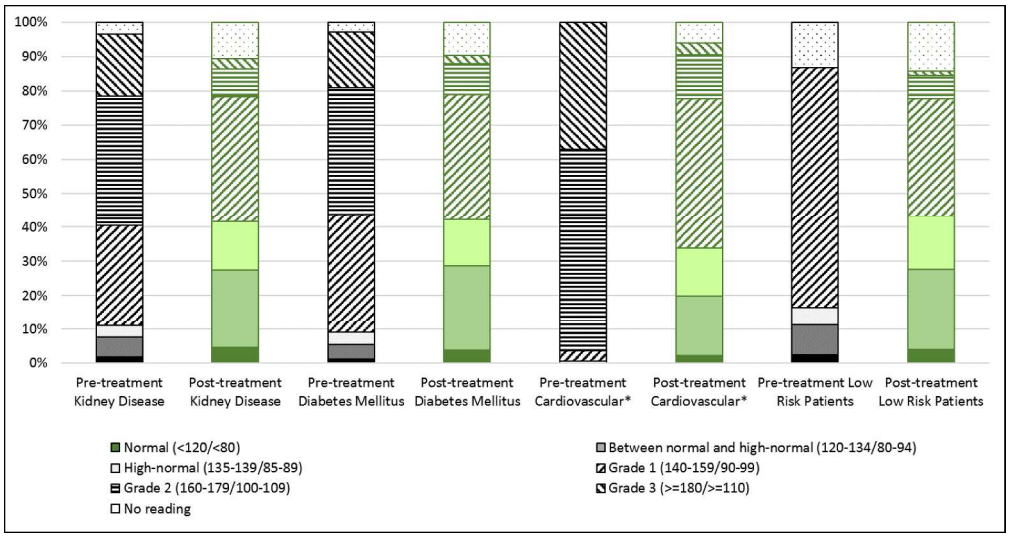

Figure 1. Percentage of patients in each blood pressure control group, pre- and post-treatment initiation, by risk cohort

248x130mm (300 x 300 DPI)

THIN Database Study Plan:

Initial Treatment of High Risk Hypertension Patients: ARB Monotherapy versus FDC Therapy

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CONTENTS

1. Motivation

Hypertension is one of the most common diseases in the world, affecting an estimated 20% of the adult population overall. It is also one of the most significant, single, modifiable risk factors in cardiovascular disease, and appropriate treatment has the potential to reduce cardiovascular morbidity and mortality significantly. The treatment pathway for patients with hypertension varies from country to country but European guidelines stress the importance of monotherapy and fixed-dose combination (FDC) therapy (Figure 1). They suggest that most hypertensive patients can only achieve effective BP control by a combination of at least two antihypertensive drugs (Mancia 2009).

Figure 1. Monotherapy versus combination therapy strategies (ESC/ESH Guidelines; Mancia et al. 2007)

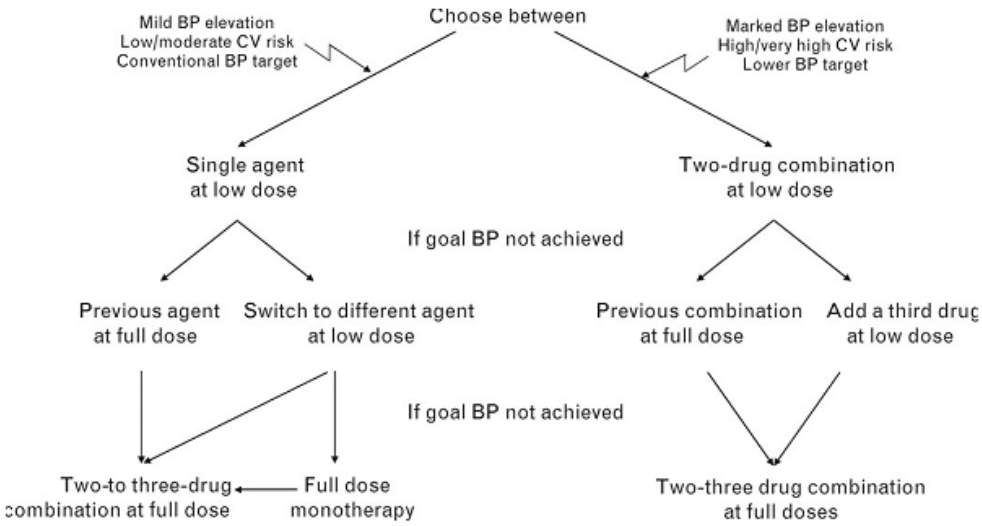


Figure 3 Monotherapy versus combination therapy strategies.

Guidelines and best practices vary for subgroups of patients. Some—such as those who present with higher grade hypertension and/or significant cardiovascular risk factors—may be good candidates for initial FDC therapy. Others—such as those who present with lower grade hypertension and fewer cardiovascular risk factors—may be able to delay movement to FDC, thereby potentially reducing their exposure to negative metabolic effects of some diuretics.

PHMR Associates has been asked by Takeda (Europe) to conduct UK healthcare database analyses to provide a better understanding of the population that may benefit from Azilsartan Medoxomil—a new angiotensin-receptor blocker (ARB)—in the treatment of Essential Hypertension. Identifying a potential initial Azilsartan Medoxomil FDC population and an Azilsartan Medoxomil monotherapy population will highlight care improvement and cost savings opportunities for subgroups of patients and permit more selective marketing to physicians and payers in charge of such patients. More generally, however, the research will provide information on how closely physicians treating high risk patients adhere to guidelines for initial treatment of hypertension and how treatment protocols affect outcomes.

2. Objectives and Specific Aims

Research Objectives

The objectives of the study are: (1) to determine which patients are good candidates for initial treatment with two-drug fixed combination therapy at low dose, rather than monotherapy (e.g., individuals with more severe hypertension), and which patients would benefit from prolonged ARB monotherapy (e.g., patients at risk of developing diabetes); (2) to examine the divergence, if any, between recommended treatment and treatment provided in practice; and (3) to consider the effect upon reaching target blood pressure goals of different treatment regimens for high risk subgroups of patients.

Specific Aims

Specific research questions (D=descriptive analysis; R=regression analysis) include:

a) What percentage of newly diagnosed patients meet guideline-derived criteria for initial treatment with FDC (e.g., patients with high index BP and/or CV risk factors)? What percentage of such patients are treated with initial FDC therapy? (D)

b) What percentage of newly diagnosed patients meet guideline-derived criteria for avoidance of FDC therapy (e.g., patients at risk of diabetes, metabolic syndrome, etc.)? What percentage of such patients are treated with initial ARB/other monotherapy? (D)

c) Among newly diagnosed patients, what percentage change therapy within the first year post-diagnosis? What percentage switch from an ARB to another ARB? What percentage switch from ARB monotherapy directly to FDC therapy? What is the difference in mean time-to-switch between those who try more than one ARB treatment regime and those who switch from ARB monotherapy to FDC treatment? (D)

d) Which observable patient characteristics (e.g., age, sex, baseline BP range, clinical conditions, BMI, etc.) are associated with initial FDC treatment (versus initial monotherapy treatment) in practice? (R)

e) How are different treatment regimes (e.g., ARB monotherapy, FDC, etc.) associated with achieving blood pressure target levels in practice, controlling for patient characteristics? (R)

3. Disease Background

The International Society of Hypertension and World Health Organization define hypertension as a sustained blood pressure (BP) of ≥140/90mmHg for most patients (but lower for diabetic patients at ≥130/80mmHg). Hypertension is graded according to blood pressure ranges. Treatment recommendations vary with grade (Table 1).

Table 1. Grades of hypertension and associated treatment recommendations

Blood pressure (BP) category	Systolic BP mm Hg	Diastolic BP mm Hg	Lifestyle intervention	Drug therapy
Normal	<120	<80	–	–
High-normal	135–139	85–89	Yes	Consider*
Mild hypertension (grade 1)	140–159	90–99	Yes	Consider†
Moderate hypertension (grade 2)	160–179	100–109	Yes	Yes
Severe hypertension (grade 3)	⩾180	⩾110	Yes	Yes

*Drug therapy may be indicated for people with established cardiovascular disease, chronic renal disease, or diabetes with complications at BP levels > 130/80 mm Hg.
†Drug therapy is recommended for people with established cardiovascular disease or diabetes or evidence of target organ damage or a 10 year cardiovascular risk ⩾ 20%.

Source: Joint British Societies (2005).

Essential (primary) hypertension is diagnosed when no identifiable cause can be found and accounts for 95% of all cases of hypertension. Secondary hypertension, where a cause can be identified, accounts for less than 5% of cases. In classic essential hypertension both the systolic and diastolic blood pressures are high, but isolated systolic and isolated diastolic hypertension are also seen. Malignant or accelerated hypertension is associated with a rapid rise in arterial pressure and, if untreated, results in rapid end-organ damage and death. The term "benign" essential hypertension has been used to describe a less aggressive form of hypertension but this term is not widely accepted because the condition is not benign. It is associated with significant morbidity and mortality. Resistant hypertension is used to describe cases of hypertension that are refractory to standard medical therapy (three different classes of anti-hypertensive drugs) (Forbes et al. 2010).

Hypertension can be broadly classified as "high renin" or "low renin". Correspondingly, there are two categories of antihypertensive drug, those which inhibit (ACE inhibitors, ARBs and beta-blockers) and those which do not inhibit (calcium channel blockers (CCBs) and diuretics) the renin-angiotensin system. Renin-profiling studies have demonstrated that younger people of <55 years and Caucasians tend to have higher renin levels relative to older people (≥55years) or the black population (of African descent). Thus, drugs which reduce BP at least in part by suppressing the renin–angiotensin system at one point or another are generally more effective as initial BP-lowering therapy in younger Caucasian patients. In contrast, CCBs and diuretics are less effective as initial BP-lowering therapy in these patients, and are better used first-line in older Caucasians or the black population of any age. ARBs remain 2nd/3rd line therapies, mainly due to the availability of cheaper alternatives such as ACE inhibitors. However this may change to 1st/2nd line when ARBs become generic (Forbes et al. 2010).

The Health Survey for England reported the prevalence of hypertension to be 3.3% in those aged under 40 years, 27.9% in those aged 40–79 years and 49.9% in those aged over 80 years. Similar figures are seen throughout the developed world, but these data probably underestimate the true prevalence of hypertension in the population owing to poor identification of cases (Forbes et al. 2010).

Hypertension contributes significantly to an individual's risk of cardiovascular disease but must be considered in the context of other cardiovascular risk factors. The risk to an individual may also correlate with the severity of the hypertension. Overall, hypertension

has been estimated to confer a 3–19% increase in the risk of stroke and a 3% increase in the risk of developing heart failure. It may account for 25% of deaths from coronary artery disease. Patients with hypertension and co-morbid diabetes, obesity or hyperlipidemia have been found to be at even higher risk for cardiovascular disease and organ damage. Hypertension is associated with marked morbidity and mortality and places a high burden on health care systems (Forbes et al. 2010).

4. Azilsartan Medoxomil

Azilsartan (TAK-491) is a highly selective, long acting angiotensin II receptor blocker (ARB) that can be used alone or in combination. The target product profile for Azilsartan monotherapy is that it will exhibit best in class attributes (superior BP lowering to olmesartan by 3-5 mmHg SBP), true 24 hour BP control with QD dosing, and safety profile comparable to other ARBs. The fixed dose combination (FDC) of Azilsartan with chlortharidone (CLD) will also exhibit best in class attributes for BP lowering, demonstrated 24-hour BP control, and safety profile comparable to other FDC's (ARB/HCT).

Azilsartan will be launched into a crowded and highly competitive antihypertensive ARB market. At Azilsartan's launch approximately 85% (volume) will be brands, but will drop to 7% 5 years later. Combination therapy (ARBs with diuretics) continues to grow. The brand vision is that Azilsartan creates additional opportunities for grade 2-3 hypertensive patients with additional risk factors to avoid life-altering events due to complications of their disease.

5. Cegedim's THIN Electronic Medical Record Database

The Health Improvement Network ('THIN') database is a computerised database of anonymised longitudinal medical records from UK primary care practices using the ViSion computer system (In Practice Systems, London, UK) to manage patient records. Currently, 479 practices participate. Data are available for a total of 9.15 million patients since 1985, including 3.36 million active cases. As of 2009, the dataset covered 5.7% of the UK population (CSD Medical Research 2011a). Data are collected on patient demographics and practice enrolment dates, diagnoses (recorded using the Read Clinical Classification version 2), referrals to secondary care (including hospital admissions and discharge diagnoses/medication data), prescriptions (recorded using the Multiflex coding system), anonymised free text, and postcode-level geographic information on socioeconomic, ethnicity and environmental variables (CSD Medical Research 2011b). Some laboratory results and measurements taken during patient visits are also recorded in THIN (Lewis et al. 2007).

THIN is a relatively young database. However, there is some historical overlap in practice sites with the well-validated GPRD database. Lewis et al. (2007) tested the strength of several well-known clinical associations in the THIN database and compared results from GPRD practices with those in non-GPRD practices. They concluded that data were equally valid in the two subsets. At least one study has attempted to externally validate data reported by primary care practices participating in the THIN data collection scheme.

Maguire, Blak and Thompson (2009) studied the reliability and timeliness of mortality reporting and developed a THIN practice-level data quality initiative. The Acceptable Mortality Reporting (AMR) indicator gives the year from which the practice is determined to reliably report all-cause mortality. Bourke, Dattani and Robinson (2004) evaluated the potential suitability of the THIN database for medical and pharmaceutical research. They concluded that data quality is assessable and that by implementing strong quality assurance procedures, THIN database records should be highly suitable for research. Since then, several studies have verified the utility of the THIN database for research on particular diseases.

The THIN database has been used in a high profile study of quality of care for patients with hypertension (Serumaga et al. 2011). MacDonald and Morant (2008) compared prevalence and treatment of clinically documented hypertension in the THIN database with that reported based on BP readings taken during a single visit as part of the Health Survey for England (HSE) in 1998 and 2003. They found lower prevalence in THIN database subjects than in the HSE. This may be partly explained by under-diagnosis and treatment of hypertension in the population.

Of particular relevance to the present proposed study, Harrison, Lancashire and Marshall (2008) investigated terminal digit bias in blood pressure readings (that is, the tendency to round the final digit of systolic and/or diastolic blood pressure readings to a round number, potentially leading to misclassification of hypertension severity) using the THIN database. They found that the extent of the problem fell dramatically over the 10 year study period from the mid-90s to mid-2000s. However, some practices continued to underestimate hypertension prevalence owing to their tendency to round the final digit of the systolic BP reading to zero.

Although demographically representative of the UK population, comparison of patients in the THIN database and the QResearch network, another UK primary care database, suggested that patients in THIN practices were more likely to be affluent (Cox et al. 2008). As socioeconomic status has been associated with health outcomes, to the extent that the THIN database is under-representative of socioeconomically deprived members of the UK general population, some findings based on THIN data should be interpreted with caution.

Approval of the THIN Scheme was granted by the NHS South-East Multi-centre Research Ethics Committee (MREC) in 2002. Studies which use only retrospective, anonymised data do not require additional MREC review. However, such studies must apply to CSD Medical Research's Scientific Review Committee for scientific approval (CSD Medical Research 2011c).

6. Study Design

Retrospective, cross-sectional, medical record database study.

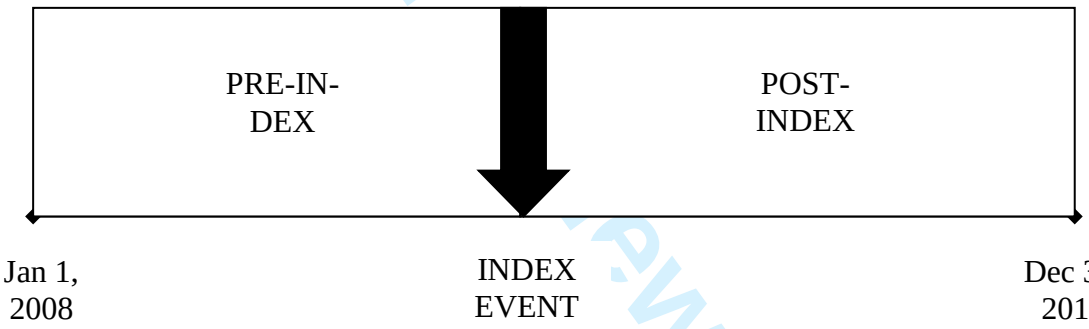
7. Study Period

Medical record data will be obtained for a three year period covering calendar years (CYs) 2008-2010. Patients will be required to be continuously registered at a practice included in the data for a minimum of 19 months during this 36 month period.

A pre-index period of a minimum of 13 months starting in January 2008 during which patients are not treated for hypertension will be sufficient to establish a 'clean' or 'treatment naive' period prior to the index event of a newly treated case of hypertension. The index date will be the date of the first prescription for an antihypertensive medication following at least 13 months free from such medication at the outset of the study period. Patients will be followed for a minimum period of 6 months post-index treatment initiation to allow time to observe the effects of treatment on hypertension outcomes (figure 2).

The use of the minimum practical study duration is recommended so as to reduce the loss of patients who are registered at practices included in the dataset for relatively short periods and may enhance the representativeness of the study population.

Figure 2. Study timeline



8. Study Population

The study population includes adults (ages 18 and older) with newly diagnosed (i.e., treatment naive) primary (essential) hypertension as identified by a Read diagnosis code in the electronic medical record (EMR) indicating essential hypertension. Patients with gestational hypertension and secondary hypertension are to be excluded.

To identify treatment naive patients, we will first select patients who were alive and permanently registered at a THIN database practice site during the study period. Patients may or may not have a diagnosis code indicating essential hypertension during the 13 month pre-index period. However, they must not have had a prescription for an antihypertensive medication during that period.

Since antihypertensive medications may be prescribed for indications other than essential hypertension, patients will be included only if they had a diagnosis indicating essential hypertension at some point during the study period and no diagnosis consistent with secondary or gestational hypertension during the same period.

Studies have shown that healthcare claims data accurately capture most patients with hypertension using diagnosis codes (Sennett 2000). The same finding would be expected with diagnoses coded in electronic medical records. This method is suggested over use of actual blood pressure readings to define hypertension since it better allows for exclusion of secondary and gestational hypertension as well as hypertensive emergencies and other causes of high blood pressure not associated with primary hypertension. However, provided that sufficient data on blood pressure readings are available in the dataset, we will confirm the diagnosis of hypertension by examining blood pressure readings from the pre-index period.

Inclusion criteria. Patients will be included if all of the following criteria are met:

- The patient is at least 18 years old at the start of the study period.
- A minimum of 19 months of continuous coverage (during a three calendar year period) in the THIN database.
- A diagnosis of essential (primary) hypertension at any point during the study period.
- A prescription for at least one antihypertensive drug (the index event) at some point after the end of the first 13 months of data and before the start of the final 6 months of data available for the patient.
- At least one blood pressure reading during the pre-index period.
- At least one blood pressure reading during the post-index period.

Exclusion criteria. Patients will be excluded if any of the following criteria are met:

- A prescription for one or more antihypertensive drugs during the 13 month pre-index period.
- A diagnosis of secondary or gestational hypertension at any time during the study period.

Sample size. TBD

9. Exposures, Outcomes, and Covariates

Exposures: Antihypertensive Pharmaceuticals

Hypertension guidelines recognize five primary drug classes: thiazide/thiazide-like diuretics, beta blockers (BBs), calcium channel blockers (CCBs), ACE inhibitors (ACEIs), and ARBs [i.e., candesartan (atacand), eprosartan (teveten), irbesartan (avapro), telmisartan (micardis), valsartan (diovan), losartan (cozaar), and olmesartan (benicar)].

This study will examine the use of the five primary classes of anti-hypertensive medications, as monotherapy or in fixed dose combinations, as well as other anti-hypertensive drugs used in general practice.

Relevant drugs will be identified using codes from Chapter 2 of the British National Formulary (BNF) as follows: thiazides and related diuretics (2.2.1), loop diuretics (2.2.2), potassium sparing diuretics (2.2.3), potassium sparing diuretics with other diuretics (2.2.4), beta-adrenoceptor blocking drugs (2.4), vasodilator antihypertensive drugs (2.5.1), centrally acting antihypertensive drugs (2.5.2), adrenergic neuron-inhibiting drugs (2.5.3), alpha-adrenoceptor-blocking drugs (2.5.4), drugs affecting the renin–angiotensin system (2.5.5), including ACE inhibitors (2.5.5.1) and angiotensin-II receptor antagonists (ARBs) (2.5.5.2), renin inhibitors (2.5.5.3), and calcium channel blockers (2.6.2).

Outcomes

Identification of FDC and monotherapy patient populations. A primary purpose of this study is to classify patients according to whether or not they would benefit from initial FDC therapy, whether or not they would benefit from remaining on ARB monotherapy for as long as possible, or neither of the above treatment protocols.

A survey of guidelines and other literature on appropriate drugs and combinations will be conducted to determine the most widely accepted treatment recommendations for sub-groups of patients with particular risk factors and comorbid conditions. Patients will be categorized accordingly in preparation for analyses.

Blood pressure control. Another outcome of interest is blood pressure control during the post-index period. Systolic and diastolic blood pressure readings will be obtained from the EMR for the period following index initiation of treatment for hypertension.

High blood pressure will be defined as readings ≥140/90 mmHg in general, and ≥130/80 mmHg for patients identified as "high risk," based upon presence of comorbid diabetes mellitus, chronic kidney disease, carotid artery disease, peripheral arterial disease, or abdominal aortic aneurysm (Rosendorff, Black, Cannon, et al, 2007).

Target blood pressure will be defined as ≥90/60 mmHg (National Heart Lung and Blood Institute, 2011) but less than the value for high blood pressure.

Patients will be identified as having high blood pressure if the most recently available measurement is in the "high" range and will be identified as being at target blood pressure if the most recently available measurement is in the target range.

Blood pressure readings will be further categorised into hypertension grade following the thresholds shown in Table 1.

Covariates

Independent Variables can be grouped into five major classes and will be constructed based upon the index date (patient demographics, socioeconomic status), pre-index period (lifestyle characteristics, illness burden, chronic/comorbid conditions), or post-index period (antihypertensive medications).

i. Patient demographics, including age, sex, and region of residence;

ii. Patient lifestyle variables, including tobacco use/smoking status, alcohol misuse, and body mass index.

iii. Socioeconomic status, as proxied by Townsend Deprivation Score (available at the patient postal code level in THIN), a composite score based on census data on assets and employment in the enumeration district or ward (Adams, Ryan and White 2005);

iv. Overall health status/illness burden as proxied by the Charlson Comorbidity Index (Deyo, Cherkin, and Ciol 1992) and following Khan et al. (2010) to map the relevant diagnosis codes from ICD-9 to Read codes;

v. Chronic conditions, including diabetes mellitus, chronic kidney disease, carotid artery disease, peripheral arterial disease, abdominal aortic aneurysm, hyperlipidemia, stroke, ischemic heart disease, and congestive heart failure; and

vi. Hypertensive medications prescribed, including ace inhibitors, ARBs, beta-blockers, calcium channel blockers, thiazide/thiazide-like diuretics, other antihypertensive drugs, and combination therapies.

10. Statistical Analysis

The proposed methods comprise a mix of descriptive analyses and logistic regression analyses.

1. Guideline review: Conduct a review of UK/European and other relevant guidelines and summarize key recommendations with particular emphasis on recommendations pertaining to initial treatment with FDC therapy and contraindications to FDC therapy. This will provide information on current clinical best practices in the treatment of newly diagnosed hypertension and identify exceptions to standard recommendations based on clinical findings and other important patient characteristics.

2. Descriptive analysis: To better understand the potential market for Azilsartan Medoxomil in fixed dose combination versus ARB monotherapy, determine the percentage of newly diagnosed patients that are indicated for initial FDC treatment and the percentage of patients who would benefit from sustained ARB monotherapy.

    a. Use the THIN medical record database to identify the number of newly diagnosed/treated patients with risk factors indicating the potential need for initiation with fixed dose combination therapy according to clinical guidelines. Identify patients with markedly elevated BP and those who are at high or very high risk of cardiovascular complications.

        i. Compute the percentage of such patients from among all patients eligible for ARB therapy owing to elevated BP and cardiovascular risk.

        ii. Compute the percentage of patients in this FDC risk group who are treated initially with FDC (versus monotheraphy) and compare this to the percentage of patients who are not in the FDC risk group who are treated initially with FDC (versus monotherapy).

    b. Use the THIN medical record database to identify the number of newly diagnosed/treated patients with risk factors indicating that FDC therapy would not be optimal (e.g., patients with, or at risk of developing, diabetes).

        i. Compute the percentage of patients who are indentified as being poor candidates for FDCs from among all patients eligible for ARB therapy owing to elevated BP and cardiovascular risk.

        ii. Compute the percentage of patients in this risk group who are treated initially with monotherapy (versus FDC) and compare this to the percentage of patients not in this risk group who are treated with monotherapy (versus FDC).

    c. Compute the percentage of patients who try multiple ARBs prior to switching to FDCs and the percentage who switch directly from an ARB to an FDC during the study period. Compute mean time-to-switch between groups of patients who switch between ARBs versus switching from an ARB directly to an FDC.

3. Multivariate analysis: To better understand which patient characteristics are predictive of initial FDC therapy versus sustained monotherapy,

    a. Prior to conducting multivariate adjusted analyses, descriptive statistics of all independent and dependent variables will be provided. Differences in means will be examined using t-statistics and differences in categorical variables will be examined using chi-square statistics.

b. Logistic regression analysis will be used to examine which patient characteristics (e.g., age, sex, baseline BP range, clinical conditions, BMI, etc.) are associated with initial FDC treatment (versus initial monotherapy treatment) in practice.

c. Logistic regression analysis will be used to estimate the relationship between different treatment regimes and BP goal outcomes, controlling for patient characteristics and time from diagnosis to most recent BP reading. If sufficient data exist, separate models will be estimated for patients who are expected to benefit from initial FDC therapy and those who may be advised to avoid FDC therapy.

11. Limitations of the Study Design, Data Sources, and Analytic Methods

In addition to the usual limitations of retrospective analyses based on medical records that were collected for administrative purposes rather than for research, there are several potential pitfalls of the proposed analyses. These may limit the ability of phmr to undertake the analyses as specified above and/or may limit the robustness and generalisability of findings. Although we will endeavour to obtain information on the data limitations prior to data acquisition, some issues may not become fully apparent until data have been acquired and data processing begins.

Potential pitfalls include the following:

- Cell sizes may be limited owing to relatively small numbers of newly diagnosed patients with high risk characteristics in the data.
- Lack of complete data from inpatient and other encounter types may limit our ability to identify high risk patients.
- Missing data on BMI and lifestyle factors may limit the regression analyses.
- Insufficient data on blood pressure readings prior to diagnosis and later in the study period may limit analysis on the relationship between treatment regimen and success in meeting blood pressure goals.
- Given that most patients with primary hypertension are ages 40 and older, it is likely that a relatively small portion of the study population will be ages 18-39, and individuals in this cohort will be unrepresentative of the market as a whole. Consequently, it may be sensible to limit analyses to middle age and older adults.

12. Plans for Disseminating and Communication Study Results

The investigators and sponsors are committed to wide dissemination of the study findings. The study plan approved by the sponsors includes a timeline for submitting abstracts to major European and international cardiovascular and hypertension society meetings. This plan also includes a provision for one or more manuscripts to be prepared and submitted for peer-reviewed academic publication. The STROBE guidelines for reporting observational studies will be followed (von Elm et al. 2007).

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **[See the title, page 1, and 'design' section of the abstract, page 2]**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **[See 'primary and secondary outcome measures' and 'results' sections of abstract, page 2]**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **[pages 4-5]**
Objectives	3	State specific objectives, including any prespecified hypotheses **[final paragraph of the 'introduction' section, page 5]**
Methods		
Study design	4	Present key elements of study design early in the paper **[pages 5-9]**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **[page 5]**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **[pages 6-7]**
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed **[n/a]**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **[pages 7-8]**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **[pages 7-8]**
Bias	9	Describe any efforts to address potential sources of bias **[See page 8 with more information included in the 'study limitations' section, page 22]**
Study size	10	Explain how the study size was arrived at **[See page 6 and 'study population' under 'results', page 9]**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **[page 9]**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **[page 9]**
		(*b*) Describe any methods used to examine subgroups and interactions **[pages 8-9]**
		(*c*) Explain how missing data were addressed **[page 9]**
		(*d*) If applicable, explain how loss to follow-up was addressed **[n/a, the study inclusion criteria stipulated that all patients were required to have 6 months follow up in the data]**
		(*e*) Describe any sensitivity analyses **[n/a]**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **[page 10]**
		(b) Give reasons for non-participation at each stage **[n/a]**
		(c) Consider use of a flow diagram **[n/a]**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **[page 10 and table 1]**

		(b) Indicate number of participants with missing data for each variable of interest **[Table 4]**
		(c) Summarise follow-up time (eg, average and total amount) **[n/a, study restricted to 6 month follow up period available for all participants]**
Outcome data	15*	Report numbers of outcome events or summary measures over time **[Tables 2 and 4]**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **[Tables 3 and 5]**
		(*b*) Report category boundaries when continuous variables were categorized **[Tables 3-5]**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **[n/a]**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **[n/a]**
Discussion		
Key results	18	Summarise key results with reference to study objectives **[Page 19]**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **[Page 22]**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **[Pages 19-21]**
Generalisability	21	Discuss the generalisability (external validity) of the study results **[Page 22]**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **[See 'funding' and 'competing interests' data uploaded with submission]**

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.