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Relationship between initial therapy and blood pressure control for high-risk hypertension patients in the UK: a retrospective cohort study from the THIN general practice database

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ABSTRACT
Objective To examine the 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 and 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 versus 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 pretreatment) 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 to 1.42) but, surprisingly, were less likely than patients with no risk factors to receive combination therapy (OR: 0.53; 95% CI: 0.47 to 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 National Institute for Health and Care Excellence 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 National Institute for Health and Care Excellence guidelines on choice of therapeutic agents among particular subgroups of the population and whether these choices affected outcomes in clinical practice.

INTRODUCTION
Hypertension—generally defined by sustained blood pressure (BP) ≥140/90 mm Hg—is one of the most common premorbid conditions contributing to deadly disease in the UK. 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 high-income 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 comorbid diabetes, obesity or hyperlipidaemia have been found to be at even higher risk for cardiovascular disease and end-organ damage. Hypertension places an extraordinarily high economic burden on healthcare systems through the high-income world.

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 UK, physicians are advised to start patients on monotherapy and add an additional drug only in the case of failure to reach BP goal on an adequate dose of a single drug. The European guidelines have for more than a decade emphasised the importance of considering additional co-occurring cardiovascular, renal and metabolic conditions when initiating treatment for hypertension, recommending different strategies depending on overall cardiovascular risk.

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-risk and high-risk individuals. Our aim is to determine whether particular subgroups of patients (eg, 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 BP goals following therapy initiation.

**METHODS**

To investigate initial therapy for new onset hypertension in the UK, we acquired patient-level data from The Health Improvement Network (‘THIN’), a computerised database of anonymised longitudinal medical records covering approximately 500 UK primary care practices, over a 3-year period, from 2008 to 2010.

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

Approval of the THIN Scheme was granted by the NHS South-East Multicentre Research Ethics Committee (MREC) in 2002. 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 STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines for cohort studies (checklist included as a web supplement).

**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 BP 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 BP not associated with primary hypertension.

To identify newly treated hypertension, we imposed a preindex ‘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 recognise five primary drug classes: thiazide/thiazide-like diuretics, beta-blockers, calcium channel blockers (CCBs), ACE inhibitors (ACEIs) and angiotensin receptor blockers (ARBs). This study examined the use of the five primary classes of antihypertensive medications, as mono-therapy or in combination, as well as other antihypertensive drugs used in general practice. Relevant drugs were identified using codes from Chapter 2 of the British National Formulary.

**BP control outcomes.** Systolic and diastolic BP readings were obtained from the EMR. The last recorded measurement during the periods immediately prior to treatment initiation (pretreatment period) and in the 6 months following treatment initiation (post-treatment period) were used to categorise patients into hypertension grade, preindex and postindex. A patient was classified into the highest grade appropriate based on either their systolic or diastolic reading. BP was defined as ‘in control’ or
‘out of control’ in the post-treatment period depending on BP readings in relation to the threshold target recommended by the National Institute for Health and Care Excellence (NICE) of 140/90.

Covariates. Independent variables were constructed based on the index date (patient demographics and socioeconomic status) or preindex 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 preindex 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 hyperlipidaemia.

Risk cohorts
Patients were assigned to risk groups based on a combination of their pretreatment BP grade and the presence of comorbid conditions following criteria outlined by Mancia et al.11 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 pretreatment hypertension grade of 2 or 3 or if BP was in the high-normal to mild range in the presence of one or more key cardiovascular conditions (ie, coronary heart disease, cerebrovascular disease, peripheral vascular disease, myocardial infarction or hyperlipidaemia). 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
The UK medical records typically provide nearly complete data for the key study variables identified here. The UK ‘Quality and Outcomes Framework’,29 introduced in 2004, provides financial incentives for the UK GPs 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 BP in hypertensive patients every 9 months, at a minimum. For patients with diabetes or kidney disease, additional incentives are offered to regularly monitor BP 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 patients 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 BP 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, V.9.3 for Windows. Simple descriptive statistics were included to illustrate characteristics of the population, initial treatment regimen, and BP control status in the 13-month pretreatment 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 BP recorded as this was necessary to evaluate the outcome of BP 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 ORs. Statistical significance of independent variables in each model was evaluated at the α<0.05 level. Bonferroni correction was used to maintain this family-wise error rate in the presence of multiple pair-wise comparisons.

A sensitivity analysis was performed to assess the potential impact of missing data on BP readings. The BP control regression analysis was rerun twice for each risk group and for all patients: under the first scenario, we assumed that all patients with missing BP readings had achieved BP control following treatment; under the second scenario, we assumed that they had not.

RESULTS
Study population
A total of 48131 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 summarises 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 pretreatment BP 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 pretreatment 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 ACEIs, followed by CCBs.
Table 1  Age and sex distribution of the study population (%)

|                        | High-risk patients | Low-risk patients | All patients |
|------------------------|--------------------|-------------------|--------------|
|                        | Kidney disease     | Diabetes mellitus | Cardiovascular* |                  |
| 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, %                | 42.0               | 58.2              | 50.9          | 50.5             | 50.9             |
| Obese/overweight, %    | 61.4               | 83.8              | 66.4          | 65.7             | 67.5             |
| Current tobacco use, % | 20.3               | 25.8              | 25.1          | 23.7             | 24.5             |
| Number of patients     | 3060               | 4303              | 29175         | 11593            | 48131            |
| % of patients          | 6.4                | 8.9               | 60.6          | 24.1             | 100.0            |

*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 (ie, coronary heart disease, cerebrovascular disease, peripheral vascular disease, myocardial infarction or hyperlipidaemia).

Table 2  Monotherapy vs fixed-drug or free-drug combination therapy, by risk cohort, n=48131 (%)

| Antihypertensive drug class | Kidney disease | Diabetes mellitus | High-risk cardiovascular* | Low-risk patients | All patients |
|-----------------------------|----------------|-------------------|----------------------------|-------------------|-------------|
| Combination therapy         |                |                   |                            |                   |             |
| Monotherapy                 |                |                   |                            |                   |             |
| ACE inhibitors              | 40.3           | 61.5              | 43.0                       | 36.6              | 42.3        |
| Angiotensin receptor blockers| 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         |

Columns may not sum to 100% because of rounding.
### Table 3  Odds of receiving fixed-drug or free-drug combination therapy vs monotherapy as index treatment

| Variable                      | Model 1: patient variables only | Model 2: risk groups only | Model 3: Adjusted OR (95% CI) |
|-------------------------------|---------------------------------|---------------------------|-------------------------------|
|                               | OR (95% CI)                     | OR (95% CI)               | OR (95% CI)                   |
| Age cohort                    |                                 |                           |                               |
| Age <55                       |                                 |                           |                               |
| Age ≥55                       | 0.946 (0.848 to 1.055)          | 1.114 (1.004 to 1.236)    |                               |
| Sex                           |                                 |                           |                               |
| Female                        | 1.385 (1.248 to 1.537)          |                           | 1.552 (1.404 to 1.716)        |
| Male                          |                                 |                           |                               |
| Registration with practice    |                                 |                           |                               |
| Existing patient              | 1.661 (1.301 to 2.120)          | 1.715 (1.353 to 2.174)    |                               |
| New patient                   |                                 |                           |                               |
| History of hypertension       |                                 |                           |                               |
| No prior hypertension         |                                 |                           |                               |
| Prior episode of hypertension | 1.756 (1.580 to 1.952)          |                           | 2.144 (1.938 to 2.371)        |
| Lifestyle factors             |                                 |                           |                               |
| Not current smoker            |                                 |                           |                               |
| Current smoker                | 1.245 (1.113 to 1.394)          | 1.269 (1.138 to 1.415)    |                               |
| Not obese/overweight          |                                 |                           |                               |
| Overweight                    | 0.972 (0.858 to 1.102)          |                           | 0.904 (0.801 to 1.020)        |
| Obese                         | 1.073 (0.945 to 1.218)          |                           | 0.956 (0.846 to 1.081)        |
| Comorbid conditions           |                                 |                           |                               |
| Diabetes                      | 0.812 (0.680 to 0.971)          |                           |                               |
| Kidney disease                | 1.123 (0.932 to 1.353)          |                           |                               |
| Coronary heart disease        | 2.980 (2.207 to 4.024)          |                           |                               |
| Cerebrovascular disease       | 1.692 (1.397 to 2.050)          |                           |                               |
| Peripheral vascular disease   | 0.976 (0.749 to 1.270)          |                           |                               |
| Myocardial infarction         | 5.252 (4.498 to 6.133)          |                           |                               |
| Hyperlipidaemia               | 0.916 (0.799 to 1.050)          |                           |                               |
| Pretreatment hypertension grade |                                  |                           |                               |
| Lower than grade 1            |                                 |                           |                               |
| Grade 1                       | 0.272 (0.230 to 0.322)          |                           |                               |
| Grade 2                       | 0.185 (0.157 to 0.218)          |                           |                               |
| Grade 3                       | 0.352 (0.299 to 0.415)          |                           |                               |
| No pretreatment BP reading    | 0.857 (0.693 to 1.060)          |                           |                               |
| Risk group                    |                                 |                           |                               |
| Diabetes mellitus             | 0.639 (0.530 to 0.771)          | 0.597 (0.494 to 0.721)    |                               |
| Kidney disease                | 1.035 (0.864 to 1.240)          | 0.912 (0.758 to 1.098)    |                               |
| Cardiovascular                | 0.524 (0.469 to 0.584)          | 0.527 (0.472 to 0.588)    |                               |
| Low risk                      |                                 |                           |                               |
| Number of observations        |                                 |                           |                               |
| Hosmer-Lemeshow goodness-of-fit | Pass                           | Pass                      | Pass                          |
| C-statistic                   | 0.74                            | 0.58                      | 0.65                          |

Bold text indicates statistical significance at the $\alpha=0.05$ level on a two-tailed test estimated with stepdown Bonferroni correction of p values.
Figure 1 Percentage of patients in each blood pressure control group, pretreatment and post-treatment initiation, by risk cohort. *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 (ie, coronary heart disease, cerebrovascular disease, peripheral vascular disease, myocardial infarction or hyperlipidaemia).

but generally positive, with 70.2% classified with grade 1 hypertension before treatment vs 42.5% with grade 1 or higher afterwards (figure 1). Overall, the proportion of patients who had BP readings at or below the ‘high normal’ range increased more than sixfold following treatment initiation, from 5.8% to 37.4%.

To better understand factors affecting treatment success, we modelled the likelihood of achieving BP control following treatment initiation as a function of therapeutic regimen (monotherapy vs 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 BP 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 BP 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 to 1.24) and kidney disease (OR: 1.18; 95% CI: 1.09 to 1.28) were each slightly more likely to achieve BP control than other patients.

Current smokers with cardiovascular health conditions were less likely to reach BP target (OR: 0.87; 95% CI: 0.82 to 0.92). Obesity reduced the odds of achieving goal for both cardiovascular risk patients (OR: 0.87; 95% CI: 0.82 to 0.93) and those deemed low risk (OR: 0.86; 95% CI: 0.77 to 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 to 1.18).

Across all patients and risk subgroups, the odds of achieving BP control fell with increasing hypertension grade. For the full sample of patients, we found that starting on combination therapy increased the odds of achieving BP control relative to starting with monotherapy.

We performed a sensitivity analysis to assess the potential impact of missing data on BP readings by rerunning the analyses on all patients, first assuming that all patients with missing BP readings had achieved BP control following treatment and, second, assuming that they had not. There were no substantive changes in the coefficients under either scenario, although 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 BP control goal.

**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 pretreatment...
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                           | 0.897 (0.727 to 1.107) | 0.854 (0.744 to 0.980) | 0.770 (0.730 to 0.812) | 0.785 (0.723 to 0.853) | 0.789 (0.757 to 0.822) |
| Age >55                           | 1.016 (0.867 to 1.191) | 0.942 (0.823 to 1.077) | 0.797 (0.757 to 0.839) | 0.918 (0.846 to 0.996) | 0.851 (0.818 to 0.886) |
| Sex                               |                |                   |                  |                  |             |
| Female                            | 1.016 (0.867 to 1.191) | 0.942 (0.823 to 1.077) | 0.797 (0.757 to 0.839) | 0.918 (0.846 to 0.996) | 0.851 (0.818 to 0.886) |
| Male                              | 1.103 (0.675 to 1.800) | 1.260 (0.898 to 1.769) | 1.053 (0.908 to 1.221) | 0.922 (0.743 to 1.143) | 1.032 (0.923 to 1.154) |
| Registration with practice        |                |                   |                  |                  |             |
| Existing patient                  | 1.103 (0.675 to 1.800) | 1.260 (0.898 to 1.769) | 1.053 (0.908 to 1.221) | 0.922 (0.743 to 1.143) | 1.032 (0.923 to 1.154) |
| History of hypertension           |                |                   |                  |                  |             |
| No prior hypertension             |                |                   |                  |                  |             |
| Prior episode of hypertension     | 0.790 (0.673 to 0.928) | 0.715 (0.617 to 0.829) | 0.878 (0.828 to 0.931) | 0.847 (0.772 to 0.928) | 0.843 (0.806 to 0.882) |
| Comorbid conditions               |                |                   |                  |                  |             |
| Diabetes                          | 1.061 (0.845 to 1.331) |                   |                  | 1.161 (1.085 to 1.242) |             |
| Kidney disease                    |                 |                   |                  | 1.180 (1.088 to 1.280) |             |
| Coronary heart disease            | 1.133 (0.685 to 1.875) | 0.731 (0.317 to 1.686) | 1.134 (0.841 to 1.530) | 1.605 (0.859 to 3.001) | 1.138 (0.909 to 1.425) |
| Cerebrovascular disease           | 1.034 (0.776 to 1.378) | 1.318 (0.936 to 1.858) | 1.254 (1.090 to 1.443) | 1.810 (1.314 to 2.493) | 1.278 (1.153 to 1.416) |
| Peripheral vascular disease       | 0.797 (0.585 to 1.085) | 1.097 (0.905 to 1.330) | 1.168 (0.987 to 1.382) | 0.715 (0.417 to 1.226) | 1.056 (0.944 to 1.182) |
| Myocardial infarction             | 1.103 (0.804 to 1.513) | 1.785 (1.210 to 2.633) | 1.161 (0.976 to 1.382) | 1.785 (1.349 to 2.363) | 1.315 (1.166 to 1.482) |
| Hyperlipidaemia                   | 0.976 (0.818 to 1.165) | 1.081 (0.932 to 1.255) | 1.086 (1.012 to 1.166) | 1.106 (0.991 to 1.233) | 1.078 (1.023 to 1.136) |
| Lifestyle factors                 |                |                   |                  |                  |             |
| Not current smoker                | 1.180 (0.973 to 1.431) | 0.936 (0.805 to 1.088) | 0.871 (0.821 to 0.924) | 0.998 (0.908 to 1.098) | 0.923 (0.882 to 0.967) |
| Current smoker                    |                 |                   |                  |                  |             |
| Not obese/overweight              | 0.976 (0.813 to 1.171) | 1.199 (0.981 to 1.465) | 1.112 (1.046 to 1.183) | 1.074 (0.974 to 1.184) | 1.098 (1.046 to 1.152) |
| Obese                             | 0.974 (0.796 to 1.191) | 0.971 (0.802 to 1.177) | 0.874 (0.820 to 0.930) | 0.857 (0.774 to 0.948) | 0.881 (0.838 to 0.925) |
| Pretreatment hypertension grade   |                |                   |                  |                  |             |
| Lower than grade 1                | 0.740 (0.547 to 1.001) | 0.556 (0.426 to 0.727) | 0.516 (0.328 to 0.812) | 0.589 (0.519 to 0.669) | 0.583 (0.527 to 0.644) |
| Grade 1                           | 0.416 (0.309 to 0.559) | 0.343 (0.263 to 0.448) | 0.321 (0.206 to 0.501) | 0.374 (0.239 to 0.563) | 0.374 (0.339 to 0.413) |
| Grade 2                           | 0.299 (0.216 to 0.414) | 0.184 (0.137 to 0.248) | 0.201 (0.129 to 0.314) | 0.234 (0.211 to 0.259) |             |
| Grade 3                           | 0.448 (0.263 to 0.765) | 0.330 (0.204 to 0.532) |                   | 0.333 (0.283 to 0.391) | 0.340 (0.295 to 0.392) |

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A population at risk

This study was conducted in the UK and included patients with newly treated hypertension who were taking at least one cardiovascular risk factor at the time of initiation of monotherapy. Patients were divided into groups based on whether they had diabetes, kidney disease, or both. The study found that patients with diabetes and kidney disease were more likely to achieve target blood pressure (BP) readings than those without these conditions. Starting on combination therapy increased the odds of achieving BP control compared with starting on monotherapy.

Conservative versus aggressive therapy for high-risk patients

The study found that combination therapy was associated with a higher likelihood of achieving BP control compared with monotherapy. The C-statistic for the combination therapy group was 0.62, while it was 0.64 for the monotherapy group. The Hosmer-Lemeshow test for goodness-of-fit showed that the model fit the data well. The table below shows the number of observations and the Hosmer-Lemeshow test results for each group.

| Variable | Combination therapy | Monotherapy |
|----------|---------------------|-------------|
| Number of observations | 2732 | 2732 |
| Hosmer-Lemeshow test | Pass | Pass |
| C-statistic | 0.59 | 0.64 |

Table 4

vs 13.5% post-treatment, overall. Patients with diabetes and kidney diseases were more likely than others to reach target BP readings. In addition, starting on combination therapy increased the odds of achieving BP control compared with starting on monotherapy.

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

Controlling BP for subgroups of patients with diabetes and/or chronic kidney disease is particularly important. Our results showed that combination therapy was associated with a higher likelihood of achieving BP control compared with monotherapy. However, the combination therapy group had lower rates of major cardiac events and lower rates of all-cause mortality than patients in the monotherapy group. Therefore, more aggressive initial therapy for this risk cohort may be recommended.

Following the recently published SPRINT study (a randomised trial of intensive vs standard BP control), which was halted early owing to the finding that patients with cardiovascular risk factors and high-normal or grade 1 hypertension plus at least one cardiovascular condition were at lower risk than patients in the standard arm, it is likely that target BP 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.

The cardiovascular risk group includes patients with grades 2 or 3 hypertension, as well as those with chronic kidney disease, diabetes, or both. Our results showed that patients in the cardiovascular high risk group were less likely to achieve target BP readings than patients in the standard arm. Therefore, combination therapy may be more beneficial for these patients.

Our results may suggest that combination therapy is indicated for patients with grade 2 or 3 hypertension plus at least one cardiovascular condition. Although it is common to prescribe combination therapy to patients with diabetes or kidney disease, our results showed that it was not a statistically significant predictor of achieving BP 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 rather than starting on monotherapy. However, given that NICE guidelines recommend combination therapy for patients with diabetes or kidney disease, our results showed that only 4.2% of patients started on combination therapy. The patients who may benefit most from combination therapy are those with grade 2 or 3 hypertension and/or chronic kidney disease.

Combination therapy may be more beneficial for patients with diabetes or kidney disease, as it is associated with a higher likelihood of achieving BP control compared with monotherapy. However, the combination therapy group had lower rates of major cardiac events and lower rates of all-cause mortality than patients in the monotherapy group. Therefore, more aggressive initial therapy for this risk cohort may be recommended.

Following the recently published SPRINT study (a randomised trial of intensive vs standard BP control), 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 BP 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.

The cardiovascular risk group includes patients with grades 2 or 3 hypertension, as well as those with chronic kidney disease, diabetes, or both. Our results showed that patients in the cardiovascular high risk group were more likely to achieve target BP readings than patients in the standard arm. Therefore, combination therapy may be more beneficial for these patients.

Our results may suggest that combination therapy is indicated for patients with grade 2 or 3 hypertension plus at least one cardiovascular condition. Although it is common to prescribe combination therapy to patients with diabetes or kidney disease, our results showed that it was not a statistically significant predictor of achieving BP 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 rather than starting on monotherapy. However, given that NICE guidelines recommend combination therapy for patients with diabetes or kidney disease, our results showed that only 4.2% of patients started on combination therapy. The patients who may benefit most from combination therapy are those with grade 2 or 3 hypertension and/or chronic kidney disease.

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promoting changes in both the European and the UK guidelines.

It has been found that reduction of systolic BP below 130 mm Hg is quite difficult to achieve for patients with diabetes, and a reappraisal of the European guidelines undertaken in 2009, and the most recent European Society of Hypertension / European Society of Cardiology (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. Recently adopted NICE guidelines specific to patients with diabetes, set target BP at or below 140/90 unless there is kidney, eye or cardiovascular damage, in which case the goal is to keep BP <130/80 mm Hg. Caution is urged in treating patients with diabetes 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, 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, BP 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. 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 (vs repeated BP 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 the 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 USA 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. 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 (ie, 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 (eg, drug class, dose, fixed-drug or free-drug combinations) on BP control. A longer follow-up period would also be required to assess the long-term effect on BP outcomes of initial therapy choice.

Finally, selection bias may have been introduced in the regression analyses because of the necessity of limiting analysis of BP control to patients who had a follow-up BP 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%. Replicating these analyses for the period 2012 onwards to assess potential changes in practice patterns under the more recent NICE and European 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 the 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 BP 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 (see online supplementary file 1).

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Competing interests  AJ and JP were employed by Takeda Europe, who provided funding for this study to PHMR. SW received consulting fees from PHMR to conduct the analyses and prepare the manuscript but has no ongoing conflict of interest in relation to the research results. TST has no personal, financial or institutional conflicts of interest 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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