PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	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
AUTHORS	Weir, Sharada; Juhasz, Attila; Puelles, Jorge; Tierney, Travis

VERSION 1 - REVIEW

REVIEWER	Martin Schulz DAPI and Freie Universitaet Berlin, Germany
REVIEW RETURNED	06-Jan-2017

GENERAL COMMENTS	This is an interesting study analyzing a large cohort of newly diagnosed hypertensive patients in UK general practice. My major concern is that the follow-up period of 6 months is too short to draw conclusions on potential differences in long-term benefit and to evaluate changes in drug therapy (drug class, fixed- or free drug combinations as well as dose). This should be mentioned as limitation. In addition, I do have a limited number of minor comments: For a couple of statements appropriate references are lacking eg, page 4, lines 24, 43, and 48; page 20, line 20; page 21, lines 19/20. Methods: Page 7, 2nd para: How was a change in AHT drug class between initiation and 6-months follow-up considered, analyzed and controlled for? Risk cohorts - page 8/9: Please, clearly describe the cardiovascular conditions included - see also Table 1 ff. Table 2: Combination therapy comprises both fixed- (FDC - btw: this acronym should be mentioned as well as HTN, bp and GP) and free drug combinations. Hence, FDC and other, right? Suggest as heading: Fixed- or free drug combination therapy. For ref. 4, 5, 20, and 21 an URL is appreciated.

REVIEWER	Alexander Leung University of Calgary, Canada
REVIEW RETURNED	02-Feb-2017

GENERAL COMMENTS	Weir and colleagues present a large, retrospective cohort study of

	48,131 patients with essential hypertension initiating antihypertensive treatment. Drug prescription patterns were examined, and analyzed according to various subgroups of cardiovascular risk. The association between the type of initial prescription and odds of achieving target blood pressure control after 6 months was reported. They found that initial combination therapy, as compared to monotherapy, was associated with improved blood pressure control at 6 months. However, higher risk patients were less likely to receive combination therapy compared to those at lower risk. Their manuscript is well-written and clear. MINOR COMMENTS 1. On page 21 in the second paragraph, there is a minor typographical error. The phrase “at or below140/90” is missing a space. 2. On page 5 in the last paragraph, the authors note that the present study was granted scientific approval to be conducted in March 2012, and data are from 2008-2010. The data used are considerably old, and reflect dated clinical practice (in accordance with the NICE 2006 hypertension guidelines [CG34]). Why has there been a delay of nearly 5 years from data acquisition and study approval until submission of this manuscript? 3. On page 8 in the last paragraph, the authors define multiple subgroups according to categories of risk. Is there a reference for the definitions they employed? MAJOR COMMENTS 1. The cohort was assembled according to the Read diagnosis code for “essential hypertension” from the electronic medical record. On page 6, paragraph 3, the authors indicate that “Studies have shown that healthcare claims data accurately capture most patients with hypertension using diagnosis codes” and they cite reference 14 (Sennett C. Manag Care. 2000;9[4 Suppl]:2-17). However, reference 14 does not provide any validation data and refers to ICD-9-CM coding instead. Previous validation studies using rigorous definitions to identify hypertension with administrative data, such as requiring at least 2 physician claims for hypertension within 2 years or 1 hospital discharge for hypertension have reported a sensitivity of 75% and specificity of 94% in Canada (e.g., Quan H, et al. Hypertension. 2009;54[6]:1423-8). Is there any corresponding validation study for THIN using the Read diagnosis code? If not, then the author’s claim, above, may be inaccurate and they should acknowledge the possibility of misclassification in their limitations. From what they indicate, it seems like all that was required was a single Read diagnosis code for “essential hypertension” in the electronic medical record to qualify for study entry. 2. The index date was defined by the first prescription for an antihypertensive medication following at least 13 months free from such a medication. Patients were then followed for 6 months after the index prescription and observed for treatment effects. Are the authors able to report the proportion of patients that remained on the same medication for the entire 6 month period (i.e., are their data to indicate that the patients actually filled a sufficient quantity for the

	duration of the 6 month follow-up)? Other studies have suggested a very poor adherence rate for patients treated for hypertension with 35% of individuals stopping treatment within the first half year (e.g., Vrijens B, et al. BMJ. 2008;336[7653]:1114-7). Also, how many of subjects changed medications during this initial 6 month period? If a large number of patients discontinued, changed, or escalated treatment during the 6 month period, it may be more difficult to directly attribute outcomes to initial treatment choice. 3. On page 8 in the first paragraph, the investigators defined blood pressure targets of 150/90 mmHg for patients without chronic kidney disease or diabetes, 145/85 mmHg for those with diabetes, and 140/85 mmHg for those with chronic kidney disease. These thresholds are highly unusual and I am not familiar with them. The authors state they are based on the "UK Quality and Outcomes Framework," an incentive program for physicians. I cannot find the thresholds the authors listed on the website they cite (reference 15). However, on a different website, I was able to find a document that refers to the general target of 150/90 mmHg: www.content.digital.nhs.uk/media/23131/Hypertensionv350/pdf/Hypertension_v35.0.pdf. Notably, the reference also states, "This document is not intended to be used in place of clinical guidelines." It seems that the thresholds listed are not for clinical purposes, but for reward, incentive, and remuneration. Would the authors please consider using more conventional clinical blood pressure targets (i.e., in accordance with contemporaneous NICE guidelines)? Do their results remain robust if conventional targets are applied? 4. The investigators handled missing data by dummy coding (page 9, paragraph 4). It is highly likely that data were not missing completely at random, and thus may have resulted in an inherent bias, especially for outcome ascertainment. Notably, in Table 4 (bottom row), the authors report the number of cases that had "no reading" for blood pressure, both pre- and post-treatment with 3.7 and 8.6% with missing outcome data, respectively. These numbers seem far, far lower than expected. I suspect the cohort may have been assembled in such a way that there is a higher than expected proportion of patients with follow-up, outcome data. Would the authors please clarify, in assembling the cohort, did they restrict the population to only patients who had at least 2 visits during a 6 month period? If so, a potential selection bias may have been introduced as they are not able to account for individuals who were started on treatment but later lost to follow-up and not accounted for at the 6 month follow-up appointment (e.g., due to non-adherence, treatment side-effects, etc.); there may also have been significant differences between "high" and "low" risk patients. 5. Is it possible for the authors to perform a sensitivity analysis, looking at blood pressure control rates, assuming that all patients with missing 6-month blood pressure measurements all had "uncontrolled" hypertension, and again assuming everyone had "controlled" hypertension. This would provide a general estimate as to the impact of the two possible extremes of outcome ascertainment bias due to missing blood pressure data. 6. The cohort included a total of 48,131 individuals. Why is the number of observations 44,011 in the multivariable regression models (i.e., as indicated at the bottom of Table 3)? What happened to the other four thousand individuals?

	7. On page 20 in the second paragraph, the authors indicate that "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." Are the authors able to please clarify if they actually examined this, as this seems different than what was indicated in their methods (i.e., page 8, paragraph 1)?

REVIEWER	James Sheppard University of Oxford UK
REVIEW RETURNED	09-Feb-2017

GENERAL COMMENTS	This manuscript presents a well conducted observational study examining initiation of antihypertensive treatment in patients with newly diagnosed hypertension. Predictors of treatment initiation and subsequent blood pressure control at 6 month follow-up are examined according to baseline risk. The findings suggest that patients are more likely to be started on combination therapy if they have risk factors for CVD (current smoking status, obesity, previous hypertension, stroke, MI or CHD) and combination therapy is more likely to result in a patient achieving blood pressure control at 6 month follow-up. Overall, the article clear and well written, but would benefit from some revisions to maximise the clarity of the methods and results. Main points 1. The rationale for the study is a little weak at the moment, why is it important to understand the real world practice in the treatment of newly diagnosed hypertension in the UK, in low and high risk individuals? Particularly since the real world practice study period was before the change in guidelines 5 years ago and so may not be as relevant anymore? 2. One of the main issues with analyses of routine data is how one deals with the inevitable missing data which arise. This is somewhat glossed over at the moment with a single sentence "Missing data were handled by including separate dummy variables in the regression models to indicate that information was not available". This is fine for categorical variables such as sex and history of disease, but how did authors deal with missing continuous such as age, BMI and BP? It appears as though more than 4,000 patients were excluded from the logistic regression analyses (48,131 [table 1]; 44,011 [table 2]) which implies a complete case analysis, but this is not specified on the methods. It would be helpful to give more detail on the degree of missingness for each variable in the analysis, and specifically how this was handled. 3. I don't agree with the conclusion that 'most patients seen in UK general practice are in fact high risk patients'. Blood pressure is more likely to be measured in patients at high risk, and therefore hypertension is more likely to be diagnosed and treated in these individuals. Thus, high risk patients are more likely to fulfil the eligibility criteria for inclusion in the study cohort. Many more low risk patients may be seen in practice but not have their BP measured regularly.

	4. These data do not support the suggestion than multi-drug therapy is helpful in achieving lower blood pressure targets as suggested in reference to the SPRINT trial. These analyses only examined attainment of targets at 140/90. 5. The authors may want to explain why they chose to examine data from such a short time period before the most recent guidelines were introduced. This may have been for pragmatic reasons and or resources available which is fine, but this does limit the clinical relevance of the study findings (which I realise is not a criteria for accepting publication in the BMJ Open). Minor points 1. Please give references for the statements in the introduction referring to treatment reducing morbidity and mortality in stroke and CVD, and lifestyle interventions being effective at controlling BP (they are both true but should still be backed up by references). 2. It would be helpful if the authors could provide the study protocol in the appendix for reference to readers who want to compare what was done with what was planned. The protocol should be available given the that study received approval from the THIN database Scientific Review Committee 3. Table 4 is quite difficult to follow and would perhaps be better presented as a graph. You could present each column of the table as a bar in the graph and present pre and post treatment %s within each category next to one another so the reader can clearly see the shift in hypertensive status categorisation at follow-up 4. Table 5 has significant predictors highlighted in bold typeface. Some apparently significant predictors are not highlight or referred to in the text (e.g. older age in diabetes 0.85 [0.74-0.98]). Is this a mistake or is this taking into account the Bonferroni correction? If it is the latter, please indicate this in a footnote below the tables. 5. In the discussion, the authors report the % of patients given different drug types by risk class. This should be reported in the results and could maybe be included as a table in the appendix. 6. The authors rightly point to the limitations of defining previous CVD events purely on the basis of primary care records. They should reference the following paper which suggests up to 25% of events could be missed when relying on only one data source: Herrett et al., Completeness and diagnostic validity of recording acute myocardial infarction events in primary care, hospital care, disease registry, and national mortality records: cohort study. BMJ 2013; 346:f2350

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Martin Schulz
Institution and Country: DAPI and Freie Universitaet Berlin, Germany

This is an interesting study analyzing a large cohort of newly diagnosed hypertensive patients in UK general practice.

1. My major concern is that the follow-up period of 6 months is too short to draw conclusions on potential differences in long-term benefit and to evaluate changes in drug therapy (drug class, fixed- or free drug combinations as well as dose). This should be mentioned as limitation.

We agree that a longer follow up period would have allowed us to evaluate long-term benefits as well as therapy changes and have edited the 'limitations' section of the discussion to include the following: "This study focused on outcomes in the immediate post-treatment initiation period. A longer follow up period would be needed to examine changes in drug therapy (e.g., drug class, dose, fixed- or free drug combinations) as well as the long-term effect upon blood pressure control of initial therapy choice."

In addition, I do have a limited number of minor comments:
1. For a couple of statements appropriate references are lacking eg, page 4, lines 24, 43, and 48; page 20, line 20; page 21, lines 19/20.

We have added several references to back up statements in the introduction and discussion sections.

2. Methods: Page 7, 2nd para: How was a change in AHT drug class between initiation and 6-months follow-up considered, analyzed and controlled for?

We initially considered examining the impact of changes in AHT drug class between initiation and 6-months follow up. However, given the data available, it was not possible to determine whether therapy changes were made because of adverse drug reactions or failure rapidly to meet blood pressure goal. All outcomes in this period have been attributed to the initial therapy chosen.

3. Risk cohorts - page 8/9: Please, clearly describe the cardiovascular conditions included - see also Table 1 ff.

We have added the list of included cardiovascular conditions in the 'Risk cohorts' subsection of the methods and in the footnotes to the tables and figure.

4. Table 2: Combination therapy comprises both fixed- (FDC - btw: this acronym should be mentioned as well as HTN, bp and GP) and free drug combinations. Hence, FDC and other, right? Suggest as heading: Fixed- or free drug combination therapy.

We agree that 'fixed or free drug combination therapy' is a more descriptive term here as both are included and we have edited the headings to Tables 2 and 3. We have also spelled out or removed all acronyms throughout the paper.

5. For ref. 4, 5, 20, and 21 an URL is appreciated.

We have added the requested URLs. Note that for references to the NICE Pathways (refs 20 and 21 formerly), these documents are regularly updated by NICE. The exact versions pertaining to our study period as cited are not available online at this time.

Reviewer: 2
Reviewer Name: Alexander Leung
Institution and Country: University of Calgary, Canada

Weir and colleagues present a large, retrospective cohort study of 48,131 patients with essential

hypertension initiating antihypertensive treatment. Drug prescription patterns were examined, and analyzed according to various subgroups of cardiovascular risk. The association between the type of initial prescription and odds of achieving target blood pressure control after 6 months was reported. They found that initial combination therapy, as compared to monotherapy, was associated with improved blood pressure control at 6 months. However, higher risk patients were less likely to receive combination therapy compared to those at lower risk. Their manuscript is well-written and clear.

MINOR COMMENTS

1. On page 21 in the second paragraph, there is a minor typographical error. The phrase “at or below140/90” is missing a space.

A space has been added between ‘below’ and ‘140/90’.

2. On page 5 in the last paragraph, the authors note that the present study was granted scientific approval to be conducted in March 2012, and data are from 2008-2010. The data used are considerably old, and reflect dated clinical practice (in accordance with the NICE 2006 hypertension guidelines [CG34]). Why has there been a delay of nearly 5 years from data acquisition and study approval until submission of this manuscript?

The regrettable delay in manuscript submission is owing to a combination of factors related to shifts in roles and responsibilities of key study personnel. Part way through project completion, the lead author moved to pursue new academic research opportunities in Canada and was unable to complete work on the study on a full-time basis. Despite the age of the data, we believe that our findings shed light on the way in which doctors in primary care respond to guidelines for hypertension management and how updated directives for initial treatment may be justified for subgroups of higher risk patients.

3. On page 8 in the last paragraph, the authors define multiple subgroups according to categories of risk. Is there a reference for the definitions they employed?

We have added a reference to the Mancia et al. (2013) ESC and ESH Guidelines, which note the importance of considering blood pressure readings (and goals) in light of both hypertension grade and cooccurrence of other cardiovascular, renal and metabolic conditions.

MAJOR COMMENTS

1. The cohort was assembled according to the Read diagnosis code for “essential hypertension” from the electronic medical record. On page 6, paragraph 3, the authors indicate that “Studies have shown that healthcare claims data accurately capture most patients with hypertension using diagnosis codes” and they cite reference 14 (Sennett C. Manag Care. 2000;9[4 Suppl]:2-17). However, reference 14 does not provide any validation data and refers to ICD-9-CM coding instead.

We agree that the reference based on ICD-9-CM codes may not be applicable to READ codes and have edited this sentence to remove this reference.

Previous validation studies using rigorous definitions to identify hypertension with administrative data, such as requiring at least 2 physician claims for hypertension within 2 years or 1 hospital discharge for hypertension have reported a sensitivity of 75% and specificity of 94% in Canada (e.g., Quan H, et al. Hypertension. 2009;54[6]:1423-8). Is there any corresponding validation study for THIN using the Read diagnosis code? If not, then the author’s claim, above, may be inaccurate and they should acknowledge the possibility of misclassification in their limitations. From what they indicate, it seems like all that was required was a single Read diagnosis code for “essential hypertension” in the

electronic medical record to qualify for study entry.

We used the combination of a READ code identifying primary hypertension and prescription of at least one antihypertensive medication (while excluding patients with a READ code indicating secondary hypertension). In the UK, doctors often do not record all diagnoses at every visit, if the diagnosis is already in the record. Hence, the method validated in Canadian health care encounters data is unlikely to be valid in THIN. Unfortunately, we did not have access to linked hospital admissions data for our cohort. Several prior studies used the same set of READ codes as in the present study to identify hypertension in THIN. However, I am not aware of research using external evidence to validate this method. We have added a statement to address this issue in the study limitations section.

2. The index date was defined by the first prescription for an antihypertensive medication following at least 13 months free from such a medication. Patients were then followed for 6 months after the index prescription and observed for treatment effects. Are the authors able to report the proportion of patients that remained on the same medication for the entire 6 month period (i.e., are their data to indicate that the patients actually filled a sufficient quantity for the duration of the 6 month follow-up)? Other studies have suggested a very poor adherence rate for patients treated for hypertension with 35% of individuals stopping treatment within the first half year (e.g., Vrijens B, et al. BMJ. 2008;336[7653]:1114-7). Also, how many of subjects changed medications during this initial 6 month period? If a large number of patients discontinued, changed, or escalated treatment during the 6 month period, it may be more difficult to directly attribute outcomes to initial treatment choice.

Medication adherence cannot readily be assessed using this data, 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. This has been added as a study limitation.

We initially considered examining the impact of changes in AHT drug class between initiation and 6-months follow up. However, given the data available, it was not possible to determine whether therapy changes were made because of adverse drug reactions or failure rapidly to meet blood pressure goal. We have now addressed this in the study limitations section.

3. On page 8 in the first paragraph, the investigators defined blood pressure targets of 150/90 mmHg for patients without chronic kidney disease or diabetes, 145/85 mmHg for those with diabetes, and 140/85 mmHg for those with chronic kidney disease. These thresholds are highly unusual and I am not familiar with them. The authors state they are based on the "UK Quality and Outcomes Framework," an incentive program for physicians. I cannot find the thresholds the authors listed on the website they cite (reference 15). However, on a different website, I was able to find a document that refers to the general target of 150/90 mmHg: www.content.digital.nhs.uk/media/23131/Hypertensionv350/pdf/Hypertension_v35.0.pdf. Notably, the reference also states, "This document is not intended to be used in place of clinical guidelines." It seems that the thresholds listed are not for clinical purposes, but for reward, incentive, and remuneration. Would the authors please consider using more conventional clinical blood pressure targets (i.e., in accordance with contemporaneous NICE guidelines)? Do their results remain robust if conventional targets are applied?

The targets referenced were included in the Annex to the "Quality and Outcomes Framework Achievement Data 2008/09" document. The referenced website given offered a more general link to provide information about the QOF, and we now have updated the URL to link to the referenced document directly. However, we agree with the reviewer that 140/90 is a more relevant metric to use in comparing achievement of blood pressure control across patient risk cohorts. The reference to the

QOF in the methods section was based on an earlier draft of the analysis, which was erroneously not updated to reflect the analysis presented in the blood pressure control regression (now Table 4). We thank the reviewer for catching this discrepancy and have edited the 'blood pressure control outcomes' section of the methods to correct this.

4. The investigators handled missing data by dummy coding (page 9, paragraph 4). It is highly likely that data were not missing completely at random, and thus may have resulted in an inherent bias, especially for outcome ascertainment. Notably, in Table 4 (bottom row), the authors report the number of cases that had "no reading" for blood pressure, both pre- and post-treatment with 3.7 and 8.6% with missing outcome data, respectively. These numbers seem far, far lower than expected. I suspect the cohort may have been assembled in such a way that there is a higher than expected proportion of patients with follow-up, outcome data.

Would the authors please clarify, in assembling the cohort, did they restrict the population to only patients who had at least 2 visits during a 6 month period? If so, a potential selection bias may have been introduced as they are not able to account for individuals who were started on treatment but later lost to follow-up and not accounted for at the 6 month follow-up appointment (e.g., due to non-adherence, treatment side-effects, etc.); there may also have been significant differences between "high" and "low" risk patients.

Most patients are expected to have regular blood pressure readings recorded in UK medical records data. This is a unique feature of UK records keeping thanks to "The Quality and Outcomes Framework", introduced in 2004, which provides financial incentives for UK general practitioners to appropriately document important metrics and meet selected quality process and outcome goals. For hypertension, physicians are paid incentive bonuses for recording blood pressure in hypertensive patients every 9 months, at a minimum, and are required to keep a registry of patients with hypertension being treated in their practice.

We did not restrict the cohort to only those patients with at least 2 follow up visits. All patients in the cohort had the same length of follow up. However, we did restrict the regression analyses to those with follow-up BP readings recorded. This was necessary in the analysis of BP control outcomes and we imposed the same restriction on the analysis of initial therapy choice for consistency. We have added a note in the study limitations section that missing follow up BP recordings may have introduced bias.

5. Is it possible for the authors to perform a sensitivity analysis, looking at blood pressure control rates, assuming that all patients with missing 6-month blood pressure measurements all had "uncontrolled" hypertension, and again assuming everyone had "controlled" hypertension. This would provide a general estimate as to the impact of the two possible extremes of outcome ascertainment bias due to missing blood pressure data.

We have taken the reviewer's suggestion to perform a sensitivity analysis around blood pressure control outcomes for patients with missing post-treatment blood pressure readings. Re-running the regression analysis on all patients under the assumption that all patients with missing data did not achieve blood pressure control resulted in no substantial changes to the magnitude or significance of the coefficients. Under the scenario that all patients with missing BP recordings had managed to achieve BP control resulted in a change in the significance (but not the signs or magnitudes) of the coefficients on 'prior episode of hypertension', 'current smoking status', and 'overweight' but did not have an appreciable impact on any of the other variables. We have added the sensitivity analysis to the methods and results sections and amended the note under 'study limitations' pertaining to the potential bias associated with missing post-treatment blood pressure data.

6. The cohort included a total of 48,131 individuals. Why is the number of observations 44,011 in the multivariable regression models (i.e., as indicated at the bottom of Table 3)? What happened to the other four thousand individuals?

As noted in our response to 4 above, we restricted the regression analyses to those with follow-up BP readings. This was necessary in the analysis of BP control outcomes. We felt that we should impose the same restriction on our analysis of odds of being initiated on monotherapy versus combination therapy so that the samples for the two analyses were the same and comparable. We have made this clearer in the methods section.

7. On page 20 in the second paragraph, the authors indicate that "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." Are the authors able to please clarify if they actually examined this, as this seems different than what was indicated in their methods (i.e., page 8, paragraph 1)?

We can confirm that we did actually examine this. The methods were stated incorrectly (based on an earlier draft of the analysis) and have now been edited to reflect the analyses presented here.

Reviewer: 3
Reviewer Name: James Sheppard
Institution and Country: University of Oxford, UK
Please state any competing interests or state 'None declared': I have received funding from the Medical Research Council to conduct a study examining the effectiveness of blood pressure lowering treatment using routine data from the CPRD.

This manuscript presents a well conducted observational study examining initiation of antihypertensive treatment in patients with newly diagnosed hypertension. Predictors of treatment initiation and subsequent blood pressure control at 6 month follow-up are examined according to baseline risk. The findings suggest that patients are more likely to be started on combination therapy if they have risk factors for CVD (current smoking status, obesity, previous hypertension, stroke, MI or CHD) and combination therapy is more likely to result in a patient achieving blood pressure control at 6 month follow-up. Overall, the article clear and well written, but would benefit from some revisions to maximise the clarity of the methods and results.

Main points
1. The rationale for the study is a little weak at the moment, why is it important to understand the real world practice in the treatment of newly diagnosed hypertension in the UK, in low and high risk individuals? Particularly since the real world practice study period was before the change in guidelines 5 years ago and so may not be as relevant anymore?

We have augmented the study rationale in the second last paragraph of the introductory section, citing European guidelines for hypertension management that have, for some years now, called for a more complete assessment of a patient's cardiovascular risk, beyond BP readings, in determining appropriate initial therapy.

We hope that our findings on how closely doctors in primary care followed the 2006 guidelines, which recommended conservative initial treatment for all, may spur interest in replicating this study using data from the period following the revised guidelines. We have augmented the final paragraph of the discussion to highlight this.

2. One of the main issues with analyses of routine data is how one deals with the inevitable missing data which arise. This is somewhat glossed over at the moment with a single sentence “Missing data were handled by including separate dummy variables in the regression models to indicate that information was not available”. This is fine for categorical variables such as sex and history of disease, but how did authors deal with missing continuous such as age, BMI and BP? It appears as though more than 4,000 patients were excluded from the logistic regression analyses (48,131 [table 1]; 44,011 [table 2]) which implies a complete case analysis, but this is not specified on the methods. It would be helpful to give more detail on the degree of missingness for each variable in the analysis, and specifically how this was handled.

Fortunately, data were rarely missing for key study variables. “The Quality and Outcomes Framework” provides financial incentives for UK general practitioners to appropriately document important metrics and meet selected quality process and outcome goals. This is a strength of using UK data to study conditions such as hypertension. Our data on blood pressure, BMI and tobacco use were far more complete than would be expected in other countries.

Blood pressure was not included as a continuous variable in the regression analyses. Instead, blood pressure recordings were categorized by hypertension grade using standard thresholds. Patients with missing pre-treatment blood pressure data were classified as missing (‘no pre-treatment BP reading’). This was done to avoid throwing out patients with missing data, since these data might not be missing at random.

BMI was not included as a continuous variable in the regressions but was categorized as ‘obese’, ‘overweight’ or ‘not obese or overweight’ using standard international thresholds. BMI was observed for almost all patients. In the few missing cases, the patient was assumed to be in the reference category, since the Quality and Outcomes Framework provides financial incentives for practices to keep a registry of all patients whose BMI exceeds 30 in the past 15 months.

Age was not missing for any patient, by design, because we excluded patients who were younger than 18 from the analysis.

We have augmented the methods section to include more information about the handling of missing data. We have also noted in the study limitations section that restricting the regression analyses to patients with a follow up blood pressure reading may have introduced bias.

3. I don’t agree with the conclusion that ‘most patients seen in UK general practice are in fact high risk patients’. Blood pressure is more likely to be measured in patients at high risk, and therefore hypertension is more likely to be diagnosed and treated in these individuals. Thus, high risk patients are more likely to fulfil the eligibility criteria for inclusion in the study cohort. Many more low risk patients may be seen in practice but not have their BP measured regularly.

We agree with this comment. While the Quality Framework provides an incentive for general practitioners to record blood pressure among all adults 45 and older at least once every 5 years, the incentives for more regular reporting apply to patients with established hypertension and other cardiovascular and metabolic risk factors. We have edited the sentence to read, ‘most patients treated for hypertension in UK general practice are in fact high risk patients.’

4. These data do not support the suggestion than multi-drug therapy is helpful in achieving lower blood pressure targets as suggested in reference to the SPRINT trial. These analyses only examined attainment of targets at 140/90.

We have removed the final statement suggesting that our findings would apply to lower target thresholds than were evaluated here. A more neutral statement about the possibility of more aggressive initial therapy being recommended has been added.

5. The authors may want to explain why they chose to examine data from such a short time period before the most recent guidelines were introduced. This may have been for pragmatic reasons and or resources available which is fine, but this does limit the clinical relevance of the study findings (which I realise is not a criteria for accepting publication in the BMJ Open).

We had an opportunity to obtain data for this time period and hoped that an examination of how practitioners treated index hypertension and the outcomes of that initial treatment decision, particularly for high risk patients, might help to inform future guidelines. Although the guidelines in effect during the study period have now been superseded, they were not radically altered in the intervening update in the sense that initiation on monotherapy is still recommended for most patients who are candidates for drug therapy. Moreover, our findings shed light on the way in which doctors in primary care respond to guidelines for hypertension management and how directives for initial treatment may need to be revisited for subgroups of higher risk patients.

Minor points
1. Please give references for the statements in the introduction referring to treatment reducing morbidity and mortality in stroke and CVD, and lifestyle interventions being effective at controlling BP (they are both true but should still be backed up by references).

We have added several references to back up all statements in the introduction.

2. It would be helpful if the authors could provide the study protocol in the appendix for reference to readers who want to compare what was done with what was planned. The protocol should be available given the that study received approval from the THIN database Scientific Review Committee.

We have added the original study protocol as an appendix to our submission.

3. Table 4 is quite difficult to follow and would perhaps be better presented as a graph. You could present each column of the table as a bar in the graph and present pre and post treatment %s within each category next to one another so the reader can clearly see the shift in hypertensive status categorisation at follow-up.

We agree and have removed table 4 and replaced it with a graph, as suggested.

4. Table 5 has significant predictors highlighted in bold typeface. Some apparently significant predictors are not highlight or referred to in the text (e.g. older age in diabetes 0.85 [0.74-0.98]). Is this a mistake or is this taking into account the Bonferroni correction? If it is the latter, please indicate this in a footnote below the tables.

Bold text indicates significance taking into account the Bonferroni correction. The note below the table has been edited to make this clearer.

5. In the discussion, the authors report the % of patients given different drug types by risk class. This should be reported in the results and could maybe be included as a table in the appendix.

The results by drug class are found in Table 2 in the paper. We have augmented the text to draw greater attention to the findings by drug class in monotherapy.

6. The authors rightly point to the limitations of defining previous CVD events purely on the basis of primary care records. They should reference the following paper which suggests up to 25% of events could be missed when relying on only one data source:

We have added this reference to the discussion of data limitations.

VERSION 2 – REVIEW

REVIEWER	Martin Schulz DAPI and Freie Universitaet Berlin
REVIEW RETURNED	28-Apr-2017

GENERAL COMMENTS	1. General overview: The authors examined all comments of the previous reviews and made appropriate revisions. 2. Suggestions for revision: Results: Appreciate adding Fig. 1. Suggest to describe the results of the benefit of the treatment initiation in more detail as this is a major finding of your (although cohort) study. Discussion: What are the main findings of the study? These should be presented first in the discussion part e.g., "In line with the UK guidelines, we found that the majority of patients were initiated on single drug therapy. Only a few patients were treated with combinations. Patients with diabetes and cardiovascular diseases were less likely to receive combinations when compared with patients with no risk factors. The treatment initiations show a benefit (66.8% hypertension grade 2 pre-treatment vs. 13.5% post-treatment). Patients with diabetes and kidney diseases reached more likely blood pressure goals. In addition, starting on combination therapy increased the odds of achieving blood pressure control compared with starting with mono-therapy. The conclusion that combination therapy may be indicated for patients with high CV risk may better read: our results may suggest ...

REVIEWER	James Sheppard University of Oxford, UK I have received funding from the Medical Research Council to conduct a study examining the effectiveness of blood pressure lowering treatment using routine data from the CPRD.
REVIEW RETURNED	24-Apr-2017

GENERAL COMMENTS	I am happy that the authors have now addressed my concerns. With regard to the missing data section, I still believe it is good practice to document the extent of missing data for each variable (number and proportion of patients in which data are missing) so that the reader can decide whether this might be a possible source of bias, but I will leave it to the authors/editors to decide if this should be added.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 3
Reviewer Name: James Sheppard
Institution and Country: University of Oxford, UK

I am happy that the authors have now addressed my concerns.

With regard to the missing data section, I still believe it is good practice to document the extent of missing data for each variable (number and proportion of patients in which data are missing) so that the reader can decide whether this might be a possible source of bias, but I will leave it to the authors/editors to decide if this should be added.

Response: We thank the reviewer for this feedback. As most of the variables do not have missing data, owing to study design and data quality, we have not provided the level of detail suggested for the current study. However, in general, I do agree with this point.

Reviewer: 1
Reviewer Name: Martin Schulz
Institution and Country: DAPI and Freie Universitaet Berlin

Please leave your comments for the authors below
1. General overview:
The authors examined all comments of the previous reviews and made appropriate revisions.

2. Suggestions for revision:

Results: Appreciate adding Fig. 1. Suggest to describe the results of the benefit of the treatment initiation in more detail as this is a major finding of your (although cohort) study.

Response: We have taken the reviewer's suggestion and added more detail in the section on 'blood pressure control' in the results.

Discussion: What are the main findings of the study? These should be presented first in the discussion part e.g., "In line with the UK guidelines, we found that the majority of patients were initiated on single drug therapy. Only a few patients were treated with combinations. Patients with diabetes and cardiovascular diseases were less likely to receive combinations when compared with patients with no risk factors. The treatment initiations show a benefit (66.8% hypertension grade 2 pre-treatment vs. 13.5% post-treatment). Patients with diabetes and kidney diseases reached more likely blood pressure goals. In addition, starting on combination therapy increased the odds of achieving blood pressure control compared with starting with mono-therapy.

Response: We thank the reviewer for this suggestion and have edited the text to provide a summary of key findings at the beginning of the discussion.

The conclusion that combination therapy may be indicated for patients with high CV risk may better read: our results may suggest ...

Response: We agree and have edited the text according to the reviewer's suggestion.

VERSION 3 – REVIEW

REVIEWER	Martin Schulz, PhD Freie Universitaet Berlin, Institute for Pharmacy, Dept. of Clinical Pharmacy, ABDA & DAPI, Berlin
REVIEW RETURNED	20-Jun-2017

GENERAL COMMENTS	Thanks for addressing all questions and suggestions appropriately.