PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	HYPERTENSION TREATMENT PRACTICES AND ITS DETERMINANTS AMONG AMBULATORY PATIENTS: A RETROSPECTIVE COHORT STUDY IN ETHIOPIA
AUTHORS	Berhe, Derbew Fikadu; Taxis, Katja; Haaijer-Ruskamp, Flora; Mulugeta, Afework; Mengistu, Yewondwossen Tadesse; Mol, Peter

VERSION 1 - REVIEW

REVIEWER	William K Bosu West African Health Organization, Bobo-Dioulasso, Burkina Faso
REVIEW RETURNED	24-Jan-2017

GENERAL COMMENTS	The comments are presented below. More details should be provided on the selection of the study participants. The study findings should be more thoroughly discussed, in particular the unexpected finding that poor medication adherence is not significantly associated with poor BP control. The study participants are unrepresentative of persons with hypertension in Ethiopia and so there should be more caution with comparisons with population-based studies. **General** The paper investigates the determinants associated with achieving control of blood pressure among patients with hypertension in six purposively selected hospitals in Ethiopia **Major comments** **For Clarification** 1. Define the study population more clearly. The investigators report approaching 903 general outpatients, of whom only six did not have hypertension. It is not clear if these patients were attending an outpatient hypertension clinic. The authors should clearly specify the main purpose of the hospital visits by the patients at the time of the survey.

	2. Concerning data collection methods, the authors mention interviews as well as medical records review. What informed the variables that were collected by interviews and those that were collected from records? Was duration of treatment not available from the medical records? Was it not possible to find out the reasons for non-compliance with medication through the interviews? 3. A major limitation of medical records is incomplete information. However, as seen in Table 1, information about smoking and alcohol history were available for all patients. How was this achieved? 4. Clarify at what point in the consultation process patients were enrolled into the study in the waiting area. Before or after seeing the physician? How did the interviewers obtain the patient records? 5. Is the treatment of hypertension free or subsidized in Ethiopia? Is the choice of antihypertensive medication influenced by the socioeconomic status of the patient? 6. Is there any particular reason why age and duration of therapy were entered into the regression model as continuous variables? 7. A lower BP target is justifiably used for control of hypertension in patients with diabetes. Please explain the phrase in "otherwise <140/90 mm Hg" in "(<130/80 mm Hg for DM &/or kidney diseases, *otherwise <140/90 mm Hg*)" as presented in Table 1 **Definition of variables** 8. Define terms such specialized and general hospitals, smoking and alcohol use 9. Briefly mention the elements of MMAS within this paper 10. The use of the term 'index visit' for the current visit seems inappropriate and confusing as it denotes first visit. 'Current visit' may be preferable. **Interpretation / conclusion** 11. Conclusions and recommendations such as targeting of specialized hospitals and older patients, presumable based on the study findings are somewhat bold a. Although the sampling process is non-random and so likely not representative of patients with hypertension, comparisons are made with the findings of studies of the general population. For example, the proportion with controlled BP is compared with the general

	population without caution. b. Similarly, the preponderance of females (63%) in the sample is explained as reflecting a higher prevalence of hypertension among females in the general population of Ethiopia. This is implausible considering that, in the cited article Kibret & Mesfin 2015 on the systematic review of the prevalence of hypertension in Ethiopia, six of the eight identified studies six showed a higher prevalence among males. In two of them, the difference was statistically significant. c. The findings on the proportion of controlled BP should be compared primarily with hospital-based studies in Ethiopia e.g. Gudina et al 2013; Asgedom et al 2016 and any observed differences discussed. The significantly older sample in this study compared with most population-based studies in Ethiopia should be acknowledged d. Adherence to antihypertensive medication in the present study (40%) could be compared with that of other studies in Ethiopia such as Hareri & Abebi 2013 (69%) and Ambaw et al 2012 (65%). 12. It seems ambitious to expect that two clinical visits will be sufficient to control blood pressure of hypertensive patients, particularly in the elderly population (Chowdhury et al 2013). Clinical guidelines recommend that initial antihypertensive should be at the lowest dose and then gradually increased based on the clinical response until the maximum tolerated dose is reached (Chobanian et al 2003, Kithas & Supiano 2010). Could this build-up of effective dose of antihypertensive dose not be misinterpreted as "treatment intensification"? 13. Achieving control of BP goes beyond "treatment intensification". There may be other strategies such as lifestyle modification, stress management and treatment of co-morbidities. 14. There may be differential recall among patients who knew their blood pressure at both visits and so might more readily attribute their lack of or poor control to low medication adherence. This would overestimate the odds ratio. 15. The study population, as defined, includes newly diagnosed hypertensive patients at the prior visit. In that case, such patients cannot be characterized as having uncontrolled BP and should be excluded from the multivariable analysis in Table 2. 16. Determinants such as the type of prescriber, grade of hypertension at the prior visit (rather than 'controlled BP'), medication adherence counselling, knowledge about hypertension and its treatment, distance from the hospital and number of co-morbidities (Ambaw et al 2012) are potential confounders that were not included in the analysis. 17. The authors should comment on why they did not evaluate the adequacy of the antihypertensive treatment prescribed.

	18. Are associations with 'null' odds ratios of 0.99 (age) or 1.04 (duration of therapy) reported as statistically significant predictors of achieving good BP target *clinically* significant? 19. Contrary to the findings in Table 2, poor medication adherence is reported as a possible explanation on p. 16 line 50, for uncontrolled BP at the current clinical visit. 20. In any case, it is surprising that, unlike many studies (Elperin er al 2014, Khosravi et al 2014, Krousel-Wood et al 2004), the authors did not find medication adherence to be a determinant of uncontrolled BP (p. 16 line 55). Yet, they do not proffer any explanation. **Minor comments** 21. Abbreviations should be fully explained at first mention e.g. MMAS 22. Incorporate the ethics into the body of the paper 23. Review the combined use of parenthesis ( ) and square brackets [ ] in the paper, particularly on p. 7 24. Avoid using "Tab" as an abbreviation for "Table" 25. Revise typos e.g. "per a row" 26. On p. 16 line 50, insert "poor" before "medication adherence"

REVIEWER	Prof Indiran Govender Sefako Makgatho Health Sciences University South Africa
REVIEW RETURNED	27-Feb-2017

GENERAL COMMENTS	In the conclusions the authors need to mention and take cognizance of the fact that access to specialized hospitals is limited and thus most hypertensive patients are managed in primary health care settings so suggesting that to improve hypertensive control people must be managed in specialized hospitals is not practical. Correct spelling in page 17 line 15 – should read 'men' and not 'man' Page 16 Line 27 'However, physicians may have been reluctant to intensify treatment further, because of fear for risk of too drastic BP lowering (e.g. resulting in dehydration when increasing diuretic doses)." There is no evidence for this from this study, I suggest the authors back their statement with evidence or remove this statement.

VERSION 1 – AUTHOR RESPONSE

Ref.: Ms. No. bmjopen-2016-015743

Title: HYPERTENSION TREATMENT PRACTICES AND ITS DETERMINANTS AMONG AMBULATORY PATIENTS: RETROSPECTIVE COHORT STUDY IN ETHIOPIA

Dear Dr. Edward Sucksmith,

Thank you for the positive response to our paper. We are grateful for the insightful comments of both reviewers. We provide a point-by-point discussion below and have updated the manuscript highlighting the changes.

Reviewer 1	
Name: William K Bosu	
Institution and Country: West African Health Organization, Bobo-Dioulasso, Burkina Faso	
Major comments /for clarification	
Comment 1	Define the study population more clearly. The investigators report approaching 903 general outpatients, of whom only six did not have hypertension. It is not clear if these patients were attending an outpatient hypertension clinic. The authors should clearly specify the main purpose of the hospital visits by the patients at the time of the survey
Answer	In our study 832 out of the 897 included patients reported to have come for their regular hypertension follow-up visit. The remaining 65 had had (perceived) symptoms; uncontrolled hypertension or adverse events.
Revised	*Page 6 line 12* *…... hypertension outpatient clinics, where known hypertensive patients come for regular follow-up visits.* *Page 6 line 17-18* *We verified in each clinic log-book (if available), and from the individual patient medical records if patients met the inclusion criteria as they had indicated during the interviews.* *Page 11 line 5-7* *The majority of included patients (93%) reported to have come for their regular hypertension follow-up visit. The remaining 7% had (perceived) symptoms; uncontrolled hypertension or adverse events.*
Comment 2	Concerning data collection methods, the authors mention interviews as well as medical records review.
Comment 2.1	What informed the variables that were collected by interviews and those that were collected from records?

Answer	We collected through interviews data that were difficult to retrieve from clinical records, such as socio demographics, medication adherence, but also treatment duration of antihypertensive medication. Data routinely recorded in the clinical records; i.e. BP measurements, medication prescribed, and comorbid illnesses were retrieved more reliably in our view than asking such information from the patient. We have clarified in the methods which data were collected through interviews and which data through chart review.
Revised	*Revised: Page 7 line 2-6* *Data collected via interview were socio demographics, medication adherence, and treatment duration of antihypertensive medication(s). The socio demographics variables were age, sex, educational and marital status, alcohol use and smoking habits. Clinical information retrieved from medical records were BP measurements, medication prescribed, and comorbid illnesses.*
Comment 2.2	Was duration of treatment not available from the medical records?
Answer	In the preparation phase of our study, we became aware that duration of therapy was not available from the medication charts. In the tiered Ethiopian healthcare system patients are expected to visit primary healthcare facilities first, and many patients with hypertension may have been treated at such centers initially. Due to the paper-based record keeping it is not easy to track a patient's full history of hypertension treatment. For this reason, we found it more reliable to ask the patient.
Comment 2.3	Was it not possible to find out the reasons for non-compliance with medication through the interviews?
Answer	We used Morisky Medication Adherence Scale (MMAS), this validated questionnaire does not have an item to ask a patient for the reason(s) of non-compliance. Although, some of the items in the questionnaire asked for special circumstances (e.g. because of travels) or because of feeling unwell that patients did not take their medication (see also your comment 2.9). A more detailed reason may have been brought up on occasion but we did not record this systematically as we did not intend to overburden both the patients and interviewers. Nevertheless, we agree that it could have provided relevant information.
Comment 3	A major limitation of medical records is incomplete information. However, as seen in Table 1, information about smoking and alcohol history were available for all patients. How was this achieved?
Answer	These variables (smoking and alcohol history) were collected through interviews. We have clarified this as indicated above in the methods section. (see comment 2.1)

Comment 4	Clarify at what point in the consultation process patients were enrolled into the study in the waiting area. Before or after seeing the physician? How did the interviewers obtain the patient records?
Answer	The patients were interviewed before they were seen by the physician. The data collector then accessed patient records later. Usually at the end of the day at the hypertension clinic or if this was not possible on a following day using the patient's medical record number to retrieve records from the hospital's medical record archive.
Revised	*Page 7 line 2* *Included patients were interviewed in the waiting area before they were seen by the physician.*
Comment 5.1	Is the treatment of hypertension free or subsidized in Ethiopia?
Answer	Treatment of hypertension in Ethiopia is not subsidized. However, the cost of healthcare in public healthcare facilities is usually cheaper than that in private healthcare centers. Patients will pay a fee for the hospital visit and have to subsequently pay for their prescribed medication.
Comment 5.2	Is the choice of antihypertensive medication influenced by the socioeconomic status of the patient?
Answer	Our study was limited to public secondary and tertiary hospitals, where a limited number of antihypertensive agents was available. The large majority of prescribed drugs were the cheapest agents within a drug class; i.e hydrochlorothiazide (thiazides), enalapril (ACE-i), nifedipine (CCBs) and atenolol (BBs) indicated at Table 1. Other agents are available on the Ethiopian market and may be prescribed more frequently at private clinics. Nevertheless, irrespective of socioeconomic status the same drugs from each class were prescribed at the public hospitals included in our study. We did not investigate whether or not patients picked them up their medication from the pharmacy, as this was outside the scope of our study. This may indeed have been affected by socioeconomic status. Ultimately, educational status that could be seen as a proxy for socioeconomic status was not related to BP control.
Revised	Page 20 line 21-24 *Differences in socioeconomic status did not seem related with type of drug prescribed. This may have affected redeeming prescriptions at the pharmacy but we did not record that information. Nevertheless, educational status – a proxy for socioeconomic status – in our study population was not related to BP control.*
Comment 6	Is there any particular reason why age and duration of therapy were entered into the regression model as continuous variables?

Answer	We decided to analyse these variables on a continuous scale as any choice of an age cut-off may be considered arbitrary with respect to what defines an elderly population, which is relevant for predicting one's cardiovascular risk but may be very different in an Ethiopian than Western context. Even more for the duration of therapy we did not consider any compelling argument could be made for any specific cut-off. We thus felt that categorizing these variables may lead to hunting for cut-offs that show significance. However, as part of a sensitivity analysis we categorized patients at 10-year age intervals, and with arbitrary lower (<35 years) and upper (≥ 65 years) limits, in which age remained a significant determinant for BP control. Finally, the use of a continuous scale maximized our power to identify differences, see e.g. http://biostat.mc.vanderbilt.edu/wiki/Main/CatContinuous
Comment 7	A lower BP target is justifiably used for control of hypertension in patients with diabetes. Please explain the phrase in "otherwise <140/90 mm Hg" in "(<130/80 mm Hg for DM &/or kidney diseases, otherwise <140/90 mm Hg)" as presented in Table 1
Answer	We have provided an explanation for the term ''otherwise'' in the table footnote.
Revised	*Page 12 (Table 1) line 4 (footnote)* *[#]otherwise: hypertensive patients without DM or kidney disease.*
Definition of variables	
Comment 8	Define terms such specialized and general hospitals, smoking and alcohol use.
Answer	We have provided a brief explanation of these terms, based on the Health Sector Transformation Plan (HSTP) document by Ethiopian Ministry of Health. This document explains the healthcare structure in Ethiopia: specialized hospitals serve as referral for general hospitals and the general hospitals as referral for primary hospitals (Chapter 6 page 142). For alcohol use and smoking habit, participants were asked if they were active smokers or alcohol users until our survey date, i.e Smoking history (Yes [Current smokers], No [never/ex-smoker]), Alcohol use (Yes [regularly/sometimes]), No [never)
Revised	*Page 6 line 5-9* *Specialized (tertiary) hospitals are at the top tier of Ethiopian public healthcare system and serve up to five million population. The general (secondary) hospitals are estimated to serve 1-1.5 million population. Furthermore, patients including those with hypertension are usually treated first at a primary healthcare center.[18]* Page 12 (Table 1) for alcohol use and smoking Page 8 line 2-5 *For alcohol use and smoking habit, participants were asked if they were active smokers or consume alcohol until our survey date, i.e smoking history (Yes: current*

	smokers, and No: never smoke or ex-smoker), alcohol use (Yes: regularly or sometimes, and No: never consume alcohol).
Comment 9	Briefly mention the elements of MMAS within this paper.
Answer	We have briefly explained MMAS-8 in the methods section.
Revised	*Page 8 line 9-16* *The items of the scale are grouped into three aspects. The first aspect is about forgetting to take medication sometimes (Item 1), and more specifically in the past two weeks (item 2), or under special circumstances during travel/leaving home (item 4), and finally asking if medication was taken yesterday (item 5). The second aspect is about intentionally stopping or cutting back medication because of feeling worse (item 3) or because of a feeling that BP is under control (Item 6). The last aspect relates to convenience (item 7) or inconvenience frequency of difficult times to take medication (item 8).*
Comment 10	The use of the term 'index visit' for the current visit seems inappropriate and confusing as it denotes first visit. 'Current visit' may be preferable.
Answer	*The term index visit is typical jargon used in the field of (pharmaco)epidemiology, but we agree that current visit reads better and we have changed this throughout the document.*
Interpretation / conclusion	
Comment 11	Conclusions and recommendations such as targeting of specialized hospitals and older patients, presumable based on the study findings are somewhat bold
Comment 11a	Although the sampling process is non-random and so likely not representative of patients with hypertension, comparisons are made with the findings of studies of the general population. For example, the proportion with controlled BP is compared with the general population without caution.
Answer	We agree that this is a single study that does not represent the whole of the Ethiopian health system, specifically with regards to patients visiting primary health care centers, and private hospitals. Nevertheless, our data suggest that specialized hospitals serving a very large proportion of Ethiopian patients and older patients were determinants for poorer BP control. These are also an easily identifiable setting/group allowing targeted interventions. So, we think our results are still valid and valuable for improving care of a sizeable part of the Ethiopian hypertensive patient treated in hospital settings. However, we agree that our strongest finding is that patients with previously uncontrolled BP are likely to remain uncontrolled at the 'current visit' and those patients require most attention. *Thus, we have focused our main conclusion to this population, and indicated further in the discussion that comparisons with general populations should be made cautiously.*

Revised	*Page 2 line 18-21 (In the abstract)* *The findings suggest the need for in-depth understanding and interventions of the identified determinants such as uncontrolled BP on consecutive visits, older age, and type of type of hospital.* *Page 18 line 5-7* *However, comparing our results with population based studies in western countries or those in other part of Africa should be done with caution as we investigated regional Ethiopian hypertensive population treated at a hospital setting.* *Page 21 Line 3-7 (conclusion)* *To improve care for patients visiting Ethiopian hospital hypertension clinics, focus should be on older patients and interventions may be needed for specialized centers.*
Comment 11b	Similarly, the preponderance of females (63%) in the sample is explained as reflecting a higher prevalence of hypertension among females in the general population of Ethiopia. This is implausible considering that, in the cited article Kibret & Mesfin 2015 on the systematic review of the prevalence of hypertension in Ethiopia, six of the eight identified studies showed a higher prevalence among males. In two of them, the difference was statistically significant.
Answer	We have revised the discussion section to make this more clear. Mixed findings have also been reported, but these differences may not be explained by studies being performed in the community or hospital setting. Ultimately, this finding is not that relevant for the main aim of our study, as gender did not determine achieving BP treatment goals.
Revised	Page 19 line 19-22 *However, a meta-analysis including hospital-based studies showed a higher prevalence of hypertension for males.[15] Another recent hospital-based study also indicated a higher prevalence of males with hypertension.[16] We observed that women were not more likely than men to have controlled BP or their treatment intensified.*
Comment 11c	The findings on the proportion of controlled BP should be compared primarily with hospital-based studies in Ethiopia e.g. Gudina *et al* 2013; Asgedom *et al* 2016 and any observed differences discussed. The significantly older sample in this study compared with most population-based studies in Ethiopia should be acknowledged.
Answer	*We agree that these are relevant studies to compare with and have added reference to them in our discussion. The age range of patients in our study was similar to a hospital based study by the Asgedom et al.*
Revised	*Page 17 line 13-20* *The level of BP control in our study was in between that reported in two studies performed in a Southern Ethiopia hospital.[16,23] Gudina et al studied the*

	prevalence of hypertension among patients visiting a hospital for any reason, of patients with known hypertension 44% were controlled.[23] The study by Asgedom et al was more similar to ours with 50% of patients visiting an outpatient hypertension clinic who had been treated for at least 12 months in the study hospital.[16] The longer duration of treatment in this latter study compared to ours perhaps may explain the better level of control, considering that duration of therapy was a significant determinant in our study for BP control.
Comment 11d	Adherence to antihypertensive medication in the present study (40%) could be compared with that of other studies in Ethiopia such as Hareri & Abebi 2013 (69%) and Ambaw *et al* 2012 (65%).
Answer	*We had not included these papers in our discussion previously as these studies used a different adherence scale (a 4 point MMAS). We have added reference to these studies in our discussion, and made further reference to the reported adherence in the paper by Asgedom et al discussed above.*
Revised	*Page 19 line 7-10* *The level of adherence we observed (40% and 57% for MMAS-8 with a cut-off at > 6 and ≥ 6 respectively) was close to that reported by Asgedom et al (35% and 61% respectively).[16] Two other Ethiopian studies reported low levels of adherence although more difficult to compare as they used a 4-point MMAS.[35, 36]*
We provided combined answers for comment 12 and 15	
Comment 12	It seems ambitious to expect that two clinical visits will be sufficient to control blood pressure of hypertensive patients, particularly in the elderly population (Chowdhury et al 2013). Clinical guidelines recommend that initial antihypertensive should be at the lowest dose and then gradually increased based on the clinical response until the maximum tolerated dose is reached (Chobanian et al 2003, Kithas & Supiano 2010). Could this build-up of effective dose of antihypertensive dose not be misinterpreted as “treatment intensification”?
Answer	We agree that not all patients may be expected to be controlled after their second visit. However, especially in that situation we would expect physicians to titrate treatment up when response is insufficient. Also, e.g. European (ESC/ESH) guidelines recommend considering immediate more aggressive combination therapy in patients who are far from target and have high CV risk.[12] Thus, the fact that patients may only have recently started antihypertensive therapy does not seem a strong explanation for the lack of treatment intensification observed in our study. As we have explained under comment 8, the majority of patients in the study hospitals are expected to start medication at primary healthcare centers and are referred for more advanced care. We have cited a document with healthcare

	structure in Ethiopia: specialized hospitals serve as referral for general hospitals and the general hospitals as referral for primary hospitals (Chapter 6 page 142).[16] Therefore, we have conducted separate analyses including patients who had been on medication for at least six months assuming that these patients are no longer in the initial careful uptitration phase. The majority (94%) of participants had started treatment six or more months ago. Exclusion of the 6% of patients who had started therapy recently (<6 months ago) did not change our findings reported in Table 2. Moreover, the proportion of patients with controlled BP 303(39%) and intensified treatment 106(23%) remained similar as well (data not shown). Moreover, duration of therapy remained a significant determinant for achieving target BP and for intensifying treatment.
Revised	*Page 6 line 5-9* *Specialized (tertiary) hospitals are at the top tier of Ethiopian public healthcare system and serve up to five million population. The general (secondary) hospitals are estimated to serve 1-1.5 million persons. Furthermore, patients including those with hypertension are usually treated first at a primary healthcare center.[18]*
Comment 15	The study population, as defined, includes newly diagnosed hypertensive patients at the prior visit. In that case, such patients cannot be characterized as having uncontrolled BP and should be excluded from the multivariable analysis in Table 2.
Answer	We agree that it may take some while to reach treatment control in recently diagnosed patients. As indicated above the group of patients who were treated for less than six months was small; i.e. six percent of the total study population. We have nevertheless performed additional analyses (data not included) as described above. The results remained largely the same. Details *described under comment 12.*
Comment 13	Achieving control of BP goes beyond "treatment intensification". There may be other strategies such as lifestyle modification, stress management and treatment of comorbidities.
Answer	We agree and have added the following to the discussion.
Revised	*Page 20 line 1-2* *Poor hypertension control should be addressed in a holistic approach that includes life style modification and management of comorbid illnesses.*
Comment 14	There may be differential recall among patients who knew their blood pressure at both visits and so might more readily attribute their lack of or poor control to low medication adherence. This would overestimate the odds ratio.
Answer	During data collection, both patients and data collectors did not (yet) know the BP at their current visit as the interviews were conducted before physicians saw the patient. BP control was not identified from the interview but extracted from the patient records. We thus think that this has not affected our analyses.

Comment 15	Explained together with comment 12.
Comment 16	Determinants such as the type of prescriber, grade of hypertension at the prior visit (rather than 'controlled BP'), medication adherence counseling, knowledge about hypertension and its treatment, distance from the hospital and number of co-morbidities (Ambaw *et al* 2012) are potential confounders that were not included in the analysis.
Answer	We did not collect data on medication adherence counseling, knowledge about hypertension and its treatment, distance from the hospital. We tried also to record the type of training a prescriber (intern, GP, resident, specialist) had received, but these data turned out to be difficult to retrieve from the patient's medical chart and we thus decided to exclude prescriber characteristics from our analyses. We appreciate the suggestion to include grade of hypertension for prior visit and number of comorbidities into our analyses. We have included these in the sensitivity analyses presented in supplement table 4 and 5. Grade of hypertension turned out to be a significant determinant for BP control but not to treatment intensification. Number of comorbidities was not significant. However, as these are all post hoc analyses we have described these in the sensitivity analyses only.
Revised	*Page 9 line 14-22* *Third (for controlled BP) and fourth (for treatment intensification) sensitivity analysis were similar with Table 2 and 3 with three modified determinants. Graded hypertension (prior BP) was performed according to the stages defined by the Ethiopian standard treatment guideline for hypertension: normal BP (systolic BP <120 and DBP < 80 mm Hg), pre-hypertensive stage (systolic BP 120-139 or diastolic BP 80-89 mm Hg), stage-I hypertension (systolic BP 140-159 or diastolic BP 90-99 mm Hg), and stage-II hypertension (systolic BP ≥ 160 or diastolic BP ≥100 mm Hg).[21] These analysis also included the number of cardiometabolic comorbid illnesses as a proxy measure for more severely ill patients and age categorized in to five groups [22]. Patients with higher hypertension stages and multiple comorbid illness were hypothesized to be more difficult to treat.* *Page 15 Line 12-21* *In the sensitivity analyses for BP control (supplement Table 4) and treatment intensification (supplement Table 5), the results were mostly similar with the main analysis (Table 2 and 3) respectively. As expected, more severe hypertension stage was associated with more difficulty to achieve target BP: stage-II hypertension [(OR 0.17 [95% CI 0.09;0.35]), and stage-I hypertension [(OR 0.34 [95% CI 0.17;0.67]. However, number of comorbid illness was not significant determinants. In case of age, older age groups were less likely to achieve target BP than youngest age group (<35 years): 55-64 years old (OR 0.41 [95% CI 0.20; 0.83]) and ≥ 65 years old (OR 0.46 [95 CI: 0.22;0.93]). Supplementary analysis for treatment intensification (Supplement Table 5), gave similar results with main analysis on Table 3, where only duration of*

	therapy was positive significant determinant (OR 1.05 [95% CI: 1.02; 1.08]) of treatment intensification.
Comment 17	The authors should comment on why they did not evaluate the adequacy of the antihypertensive treatment prescribed.
Answer	We have not aimed to evaluate the adequacy, as all of the prescribed agents (ACE-I, BB, CCBs and diuretics) have demonstrated efficacy in lowering BP and reducing cardiovascular events in large clinical outcome studies. Also, their combined use is considered appropriate. We could have evaluated if in the general population diuretics and CCBs were initially prescribed as this is recommended in a black population. However, records did not always go back far enough to reliably indicate if a patient had been treated in the right order. Moreover, evaluating if patients with higher BP are prescribed more drugs is confounded by the fact that BP levels will be affected by antihypertensive therapy.
Comment 18	Are associations with 'null' odds ratios of 0.98 (age) or 1.04 (duration of therapy) reported as statistically significant predictors of achieving good BP target clinically significant?
Answer	These are continuous variables with OR reported for a change in one year. The likelihood of achieving target BP at the current visit will decrease by 1% for increasing age by one year /increase by 4% with duration of therapy. The p-values for these variables were 0.03 (age in year) and 0.001 (duration of therapy). Due to rounding the confidence intervals mention 0.99 but are 0.988 for age and 1.037 to 1.04 for duration of therapy. These findings are still relevant as more the ranges can be quite large. In supplementary analysis for comment 15 and part of 16 and 20, age categorized similar with Asgedom *et al* and shown to be significant between younger age (<35) and older groups (> 45).
Revised	*Supplement Table 4, also described under comment 16* *Page 15 line 16-18* *In case of age, older age groups were less likely to achieve target BP than youngest age group (<35 years): 55-64 years old (OR 0.41 [95% CI 0.20; 0.83]) and ≥ 65 years old (OR 0.46 [95 CI: 0.22;0.93]).*
Comment 19	*Contrary to the findings in Table 2, poor medication adherence is reported as a possible explanation on p. 16 line 50, for uncontrolled BP at the current clinical visit.*
Answer	We agree that as we did not observe a significant relation between adherence and treatment control, we should be careful in how to phrase this. Nevertheless, in individual consultations prescribers when doubting compliance of a patient to previously prescribed medication may indeed be reluctant (rightfully so!) to intensify treatment. We have adopted this section in line with your comment, recognizing this scenario. Of note, also in the hospital-based Asgedom *et al* study performed in Southern Ethiopia the relation between BP control and adherence was not significant (also

described under comment 11.c and 20)

Revised	*Page 19 line 4-14* *Moreover, prescribers may not intensify treatment if they suspect that increased BP levels may be related to a suspected or reported poor compliance for a particular patient. (Poor) medication adherence is known as an important determinant for controlling hypertension.[34] The level of adherence we observed (40% and 57% for MMAS-8 with a cut-off at > 6 and ≥ 6 respectively) was close to that reported by Asgedom et al (35% and 61% respectively).[16] Two other Ethiopian studies reported low levels of adherence although more difficult to compare as they used a 4-point MMAS.[35, 36] Surprisingly, the level of adherence was not associated with BP control in our main and sensitivity analyses (Supplement Table 1). Similarly in the study by Asgedom et al, a hospital-based study in Southern Ethiopia, no relation with adherence and BP control was observed.[16] Self-reported medication adherence may be overestimated and therefore lead to bias.*
Comment 20	In any case, it is surprising that, unlike many studies (Elperin *et al* 2014, Khosravi *et al* 2014, Krousel-Wood et al 2004), the authors did not find medication adherence to be a determinant of uncontrolled BP (p. 16 line 55). Yet, they do not proffer any explanation.
Answer	*This finding was a surprise for us too. Although our study is not the first to find such lack of relation between adherence and reaching treatment goals.*
Revised	*Page 19 line 10-14* *Surprisingly, the level of adherence was not associated with BP control in our main and sensitivity analyses (Supplement Table 1). Similarly in the study by Asgedom et al, a hospital-based study in Southern Ethiopia, no relation with adherence and BP control was observed.[16] Self-reported medication adherence may be overestimated and therefore lead to bias.*
Minor comments	
Comment 21	Abbreviations should be fully explained at first mention e.g. MMAS
Amendment	We have adopted your suggestion and carefully reread the document. Page 7-8 line 24/1
Comment 22	Incorporate the ethics into the body of the paper.
Amendment	We put the ethics in the methods section. Page 10 line 1-5
Comment 23	Review the combined use of parenthesis ( ) and square brackets [ ] in the paper, particularly on p. 7
Amendment	We have adopted your suggestion and carefully reread the document.
Comment 24	Avoid using “Tab” as an abbreviation for “Table”

Amendment	We have adopted your suggestion and carefully reread the document.
Comment 25	Revise typos e.g. “per a row”
Amendment	We have adopted your suggestions and carefully reread the document.
Comment 26	On p. 16 line 50, insert “poor” before “medication adherence”
Amendment	We have adopted your suggestion. (Page 19 line 6)
General comments	
Comment 1	More details should be provided on the selection of the study participants. The study findings should be more thoroughly discussed, in particular the unexpected finding that poor medication adherence is not significantly associated with poor BP control.
Answer	We have described the participant selection more extensively in the methods section, see also our response to comments 1 and 2). We have also addressed the surprise finding with regards to lack of association between adherence and BP control. See comment 20 of reviewer 1. Such finding is not unprecedented as indicated above. But, we did find in the additional sensitivity analyses performed on instigation of reviewer 1 that adherence was associated. This is in itself reassuring, but since this was a post hoc analysis we have been careful in our reporting. We have presented factual data in the results section and refrained from making strong statements in relation to adherence in the discussion section.
Revised	*Described under comments 1 and 2 (study participants), and comment 20 (adherence).*
Comment 2	The study participants are unrepresentative of persons with hypertension in Ethiopia and so there should be more caution with comparisons with population-based studies.
Answer	Described under comment 12

Reviewer 2

Name: Prof. Indiran Govender

Institution and Country: Sefako Makgatho Health Sciences University, South Africa

Comment 1	In the conclusions, the authors need to mention and take cognizance of the fact that access to specialized hospitals is limited and thus most hypertensive patients are managed in primary health care settings so suggesting that to improve hypertensive control people must be managed in specialized hospitals is not practical.
Answer	We agree with the comment. The majority of the population in Ethiopia receives their medical care at primary healthcare centers. We have addressed this also above in response to reviewer no.1. we have updated also our paper to indicate more clearly the study population and health care setting included.
Revised	*Appropriate changes were made throughout the paper.* *Page 2 line 19-21 (In the abstract)* *The findings suggest the need for in-depth understanding and interventions of the identified determinants including uncontrolled BP on consecutive visits, older age, and type of hospital.* *Page 6 line 5-9.* *Specialized (tertiary) hospitals are at the top tier of Ethiopian public healthcare system and serve up to five million population. The general (secondary) hospitals are estimated to serve 1-1.5 million persons. Furthermore, patients including those with hypertension are usually treated first at a primary healthcare center.[18]* *Page 21 Line 3-7 (conclusion)* *To improve care for patients visiting Ethiopian hospital hypertension clinics, focus should be on older patients and interventions may be needed for specialized centers.*
Comment 2	Correct spelling in page 17 line 15 – should read ‘men’ and not ‘man’
Amendment	We have changed this.
Comment 3	Page 16 Line 27 ‘However, physicians may have been reluctant to intensify treatment further, because of fear for risk of too drastic BP lowering (e.g. resulting in dehydration when increasing diuretic doses).” There is no evidence for this from this study, I suggest the authors back their statement with evidence or remove this statement.
Answer	We agree that we cannot back this up with any study data, and this was merely speculation on what could explain treatment intensification. We have thus removed the sentence.
Revised	Sentence removed

Editorial request:

The manuscript contains typographical/ grammatical errors (e.g. the title: "EHTIOPIA"; page 3: “insight in determinants” etc.). Please thoroughly proofread the paper.

Authors:

We have carefully reread and revised where appropriate the manuscript.

Kind regards,

Derbew Fikadu Berhe and Peter Mol, on behalf of all co-authors

VERSION 2 – REVIEW

REVIEWER	William K Bosu West African Health Organisation, Bobo-Dioulasso, Burkina Faso
REVIEW RETURNED	11-Apr-2017

GENERAL COMMENTS	General The authors have satisfactorily revised the manuscript in many places. In some cases, they have performed additional sensitivity analyses to evaluate certain findings. However, the paper can still be improved further. The script should be thoroughly revised, language made simpler and straight-to-the-point so that it is easier to read. • For example, largest populous country should be revised to most populous ….; "treatment duration of antihypertensive medication" could be revised to "duration of antihypertensive treatment. • The title still has "Ethiopia" misspelt. • Some sentences (e.g. lines 33-41 on p.17) can be split into two. Specific Observations 1. There following points could simply be added to the limitations section: a. Reasons for non-compliance were not evaluated. In some studies, the major reason for noncompliance is the inability to afford drug prices (Buabeng et al 2004). [Comment 2.3] b. The adequacy of prescribing was not assessed [Comment 17] c. Potential confounders in comment 16 that were not included in multivariable analysis d. The ambitious expectation that two clinic visits are sufficient to ensure adequate control of blood pressure. The authors' response to comment 12 is not convincing. A recent 9-year cohort study in Japan (Shima et al 2016) concluded that "uncontrolled hypertension increased significantly as the number of outpatient visits decreased" 2. Item 2 of the MMAS-8 scale in Morisky et al 2008: "Over the past 2 weeks, were there any days when you did not take your high blood pressure medicine?). The authors interpret this as "forgetting to take medication … more specifically in the past two weeks (item 2)" in comment 9. Does this item necessarily imply forgetfulness? 3. Some contradictions a. The authors indicate that patients who are referred to specialized hospitals may have more severe hypertension. Yet, the authors find it "surprising that patients in these hospitals are more likely to have inadequately controlled BP" over 2 clinic visits b. In comment 14, the authors reject possible bias from differential recall of adherence behaviour of patients who may have known their blood pressures at both visits. They argue that "both patients and data collectors did not (yet) know the BP at their current visit as the interviews were conducted before physicians saw the patient". However, on page 6, they also report that the "routine practice in the study hospitals is that nurses measure patient's blood pressure and assign the patient to a physician". Could patients not know their BP

	from this preliminary measurement by the nurses? 4. The authors retain bias relating to external validity in comment 11b. If 63% (551/897=61.4%) of the hypertensive patients who were sampled are females, it is incorrect to conclude that this implies a higher prevalence of hypertension in females in the general population. 5. In the revision under comment 11c, specify "the duration of therapy" in the two studies being compared 6. Authors should consider incorporating some of the additional analyses to the text e.g. comment 12, if these unbiased analyses can better explain the findings

VERSION 2 – AUTHOR RESPONSE

Reviewer 1	
Name: William K Bosu	
Institution and Country: West African Health Organization, Bobo-Dioulasso, Burkina Faso	
General comment: The script should be thoroughly revised, language made simpler and straight-to-the-point so that it is easier to read	
Comment	For example, largest populous country should be revised to most populous ….; "treatment duration of antihypertensive medication" could be revised to "duration of antihypertensive treatment.
Answer	Dear Dr Bosu we thank you for your thorough review of our manuscript. We have asked a native speaker (Michelle Pena) to correct the entire manuscript to improve the flow of the text. We have made changes in line with your suggestions throughout the document.
Comment	The title still has "Ethiopia" misspelt.
Answer	*Apologies, we are slightly embarrassed that we had missed this. The title is now corrected in all versions of the resubmitted document. Thank you for pointing this out.*
Comment	Some sentences (e.g. lines 33-41 on p.17) can be split into two
Answer	In our general revisit of the manuscript (see your first comment) we have also paid specific attention to lengthy sentences, and we shortened them where appropriate.
Specific observations	
Comment 1	There following points could simply be added to the limitations section
Comment 1a	Reasons for non-compliance were not evaluated. In some studies, the major reason for noncompliance the inability to afford drug prices (Buabeng *et al* 2004). [Comment 2.3]
Answer	As the reviewer indicates, we have not evaluated the reasons for non-compliance. The validated MMAS checklist does not ask for such information and as we did not want to overburden patients we did not ask for more details. We agree though with the reviewer that patients may be non-compliant because of their inability to afford drugs. We have incorporated this in the limitation section.
Revised	*Page 22 line 10-13* *We did not query patients for economic reasons of non-compliance, e.g. if they could afford their medication or that they needed to travel too far to collect medication. We used the validated MMAS-8 questionnaire and did not want to overburden patients further.*
Comment 1b	The adequacy of prescribing was not assessed [Comment 17]
Answer	Indeed, we did not study if prescribing had been in line with guideline recommendations as our goal was to study the actual impact on BP control. Nevertheless, we have added this to the limitation section as you have proposed.

Revised	*Page 22 line 4-6* *We did not study to what extent prescribing was in line with guideline recommendations, but focused instead on the actual impact of prescribing on BP.*
Comment 1c	Potential confounders in comment 16 that were not included in multivariable analysis.
Answer	We have added some of the potential confounders that you referred to in your previous comments to the limitations; such as type of prescriber, knowledge about hypertension, distance from the hospital to the limitations. However, it is important to realize that this may still not be a comprehensive list.
Revised	*Page 22 line 15-18* *Finally, as in all studies we were not able to include all previously reported potential confounders for achieving BP control [35]. For example, type of prescriber (was difficult to retrieve from medication charts), or medication counseling and patient's own knowledge of hypertension and treatment goals (would have required further interview time) may require further study.*
Comment 1d	The ambitious expectation that two clinic visits are sufficient to ensure adequate control of blood pressure. The authors' response to comment 12 is not convincing. A recent 9-year cohort study in Japan (Shima *et al* 2016) concluded that "uncontrolled hypertension increased significantly as the number of outpatient visits decreased".
Answer	We agree that not all patients can be expected to be controlled after two clinic visits. We also expected that longer durations between visits may result in less control of BP. We did see a correlation in the bivariable analyses between level of BP control and gap between visits; i.e. with longer gaps there was less BP control [table 2. OR 0.89 (95%CI: 0.82;0.97)]. However, this correlation was no longer significant when we corrected for other confounders in our multivariable model [table 2. OR 0.91 (0.82;1.02)]. In line with previous research more frequent visits, such as the Shima paper may be needed, for doctors to intensify treatment.
Revised	*Page 21 line 21-23* *In our study, level of BP control was assessed for two consecutive visits only. Follow up at more visits may be needed, as achieving BP control may require more time, and would thus provide a better understanding of doctors truly being slow to intensify treatment.*
Comment 2	Item 2 of the MMAS-8 scale in Morisky et al 2008: "Over the past 2 weeks, were there any days when you did not take your high blood pressure medicine?). The authors interpret this as "forgetting to take medication … more specifically in the past two weeks (item 2)" in comment 9. Does this item necessarily imply forgetfulness?
Answer	In our previous answer to your similar comment 9 we wrote: *The items of the scale are grouped into three aspects. The first aspect is about forgetting to take medication sometimes (Item 1), and more specifically in the past two weeks (item 2), or under special circumstances during travel/leaving home (item 4),* We agree though that we could make this even more explicit that the medication could have been forgotten or were intentionally not taken. We have added this in the description of the MMAS-8 description in the methods section.
Revised	Page 8 line 10-11 *forgetting or intentionally not taking prescribed medication*
Comment 3	Some contradictions
Comment 3a	The authors indicate that patients who are referred to specialized hospitals may have more severe hypertension. Yet, the authors find it "surprising that patients in these hospitals are more likely to have inadequately controlled BP" over 2 clinic visits.
Answer	You are right in pointing out this apparent contradiction. Patients may be referred to specialized hospitals because of comorbidities or severity of hypertension. Prolonged poor medication response may be another reason to refer patients. Hence, patients in these hospitals are more likely to have inadequately controlled BP. Still, these hospitals are meant to be well equipped with better facilities as well as more experienced staff. The level of treatment intensification seems numerically higher in specialized (27%) than in generalized hospitals (21%), although these differences are not significant in our bi-and multivariable analyses (table 3). Thus, it may be possible that despite greater efforts to treat patient other factors such as disease severity could explain the level of BP control.

	We have therefore made the following amendments in the discussion. We removed: *"Hence, it is surprising that patients in these hospitals are more likely to have inadequately controlled BP."* And added instead.
Revised	Page 19 line 11-15 *Numerically, patients received more treatment intensification at specialized hospitals (27%) than at generalized hospitals (21%), although these differences were not significant in our bi-and multivariable analyses (Table 3). Thus, the additional effort provided in these specialized hospitals may have not been sufficient to offset the difficulties in achieving BP control in the more complex patient population.*
Comment 3b	On comment 14, the authors reject possible bias from differential recall of adherence behavior of patients who may have known their blood pressures at both visits. They argue that "both patients and data collectors did not (yet) know the BP at their current visit as the interviews were conducted before physicians saw the patient". However, on page 6, they also report that the "routine practice in the study hospitals is that nurses measure patient's blood pressure and assign the patient to a physician". Could patients not know their BP from this preliminary measurement by the nurses?
Answer	You are correct in pointing out that some patients may have known their BP if they were seen by the nurse before the interview took place. However, the majority of our study participants were interviewed in the waiting area before a nurse measured their BP. The interviewers were not aware of the BP, as they did not ask for the BP during the interview. So, we think that any bias to our study is minimal. We have already added the following sentence in our previous response when patients were interviewed in the methods section.
Revised	*Page 7 line 2* *Patients were interviewed in the waiting area before they were seen by the clinic nurse or physician.*
Comment 4	The authors retain bias relating to external validity in comment 11b. If 63% (551/897=61.4%) of the hypertensive patients who were sampled are females, it is incorrect to conclude that this implies a higher prevalence of hypertension in females in the general population.
Answer	We agree that our study cannot claim any differences in prevalence of hypertension between men and woman due to the study design. We have tried to address this also in our previous answer. Nevertheless, more women than men came to our sample of hospitals, and we did not approach man or woman differently in the recruitment, nor did man refuse more often than women to participate in the study. The impact of gender on BP control or treatment intensification was not significant, so we think that the results are relevant also to settings irrespective of the prevalence of disease between men and women. We have tried to clarify even more that the higher number of women in our study sample does not imply that in Ethiopia hypertension is more prevalent in women. We have revised the paragraph on this.
Revised	*Page 20/21 line 21-24/1-5* *We found that more hypertensive women than men were included in our study, and that few patients smoked. Our study is not a population study designed to evaluate prevalence of hypertension, and the reason why more women may be included could have been that women seek more care than men. Although, a recent community-based study evaluating prevalence of hypertension in Ethiopia suggested more women were hypertensive than men, [13] a meta-analysis including hospital-based studies, [15] and another recent hospital-based study reported a higher prevalence of males with hypertension. [16] The higher prevalence of women in our study is likely of less relevance for our study findings, as gender was not a significant determinant for BP control BP or treatment intensification.*
Comment 5	In the revision under comment 11c, specify "the duration of therapy" in the two studies being compared.

Answer	These studies did not have 'duration of therapy' as a variable.
Revised	Page 18 line 20-21 Unfortunately, information on duration of the therapy was not included in these studies.
Comment 6	Authors should consider incorporating some of the additional analyses to the text e.g. comment 12, if these unbiased analyses can better explain the findings
Answer	We have added one additional analysis as supplement table
Revised	*Page 9 line 23-24* *"A fifth sensitivity analysis was in patients who had been on medication for at least six months assuming that these patients were no longer in the initial careful uptitration phase."* *Page 15/16 line 21-23/ 1-3* *The majority (94%) of participants had been on medication for at least for six months. Exclusion of the 6% of patients who had recently started therapy (< 6 months ago) in the sensitivity analysis (Supplement Table 6) did not change our findings reported in Table 2. The proportion of patients with controlled BP 303 (39%) remained similar as well. Duration of therapy remained a significant determinant for achieving target BP and for intensifying treatment.*

VERSION 3 – REVIEW

REVIEWER	William K Bosu West African Health Organisation
REVIEW RETURNED	21-Jun-2017

GENERAL COMMENTS	The authors have satisfactorily revised the manuscript in line with the second review.