PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Population impact of different hypertension management guidelines based on the prospective population-based Heinz Nixdorf Recall study
AUTHORS	Gronewold, Janine; Kropp, Rene; Lehmann, Nils; Stang, Andreas; Mahabadi, Amir; Weimar, Christian; Dichgans, Martin; Moebus, Susanne; Kröger, Knut; Hoffmann, Barbara; Jöckel, Karl-Heinz; Erbel, Raimund; Hermann, Dirk

VERSION 1 – REVIEW

REVIEWER	Augustine Kang Brown University
REVIEW RETURNED	04-Sep-2020

GENERAL COMMENTS	Overall, this is a very well-written manuscript. It describes the rationale and key details pertaining to the scientific methodology of the study hypothesis well. The topic of the paper is also timely and fills gaps in research. While I have minimal concerns for its publication, the following are a few minor points for the authors to note: 1. Please examine the entire manuscript for typos, grammar, and sentence flow in general (e.g. “Methods” is spelled incorrectly in the abstract) 2. On page 5, lines 38 to 43, it is not clear what “Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research” means, or what its significance is. If not pertinent, I suggest removing it. It is also repeated on page 6, lines 3-5. 3. Page 7, line 21 – please use numbered superscript for in-text citation of SPSS software. 4. Description of the respective guidelines should be in the methods section, not the results section.

REVIEWER	Burnier Michel Service of Nephrology and Hypertension University Hospital Lausanne, Switzerland
REVIEW RETURNED	26-Sep-2020

GENERAL COMMENTS	The authors of these analyses have used the data of treated and untreated subjects having participated in a German cohort to compare the impact of several hypertension guidelines including the the recent ACC/AHA and the ESC/ESH guidelines. Their results show that the percentage of untreated patients who would

	have been treated according to the recent US guidelines would be higher and the percentage of patients achieving target BP under treatment would be lower when following the last US guidelines. The incidence of cardiovascular events is also higher accoring to these guidelines. Comments: The idea to compare the impact of the different guidelines on a population of treated and untreated hypertensive patients is interesting. However, this set of analysis raise up few questions. 1. The first is whether it is useful to analyse guidelines that are not recommended anymore. Why not concentrate on the most recent guidelines inclu.ding the 2020 ISH guidelines that have now been published. 2. The last ACC/AHA guidelines have changed the definition of hypertension and defined new categories at much lower levels of blood pressure. Hence, it is not surprising that there are are more people to be treated and more patients with uncontrolled BP as they were not treated with this target in mind. This was already publised by Muntner et al after the publication of ACC/AHA guidelines. 3. There is one missing issue regarding the ESC/ESH recommendations. In patients with a systolic BP between 130 and 139 and diastolic between 85 and 89, treatment is recommended if patients have a very high cardiovascular risk in particular patients with corornary heart disease and cerebrovascular disease. This does not appear in the paper. 4, When comparing the different guidelines in Figure 1, it appears that in age and sex-corrected analyses there are no difference between ESC/ESH and ACC/AHA impact on 5-year cardiovascular events. This should be discussed. Indeed, in the end the difference between the two guidelines are minor because not all patients with an elevated BP according to ACC/AHA guidelines should be treated with drugs. 5. The incidence of CV events is greater when using the ACC/AHA guidelines. THis is not surprising as the number of patients concerned is greater and it is well known that cardiovascular events occurs although in patients with optimal, normal and high normal BP. The incidence rate is about 1% per year (Vasan et al, NEJM, 2001). Thus, these analyses are not really surprising MInor comments: On page 40/44, the value of diastolic BP in the no column should be corrected: 77 instead of 777

REVIEWER	Thomas Beaney Imperial College London, UK
REVIEW RETURNED	15-Oct-2020

GENERAL COMMENTS	This is an interesting paper which addresses an important and under-researched topic. Gronewold et al demonstrate significant differences that exist between hypertension guidelines based on the criteria for diagnosis. They base these findings not only on the BP threshold, but also on the characteristics of underlying cardiovascular risk. Given the wide use of hypertension guidelines around the world, this article is a welcome addition to the literature. As I mention below, I would like to see more in-depth discussion of the impact of the findings.

	In terms of statistical analyses, these are mostly well-described and appropriate, but I have one comment below. Missing data has been presented clearly, and on the whole is minimal. In the case of CIMT values, where missing data could have an impact, a sensitivity analysis has been carried out I have a few other comments and suggestions: 1. Methods p6: further description of the study cohort is required in the paper regarding the method of BP measurement (this information is currently in the appendix), but is key to interpretation, particularly given the move towards ambulatory monitoring of BP in recent guidelines. 2. Results: a summary table of the thresholds and indication for initiating treatment, and for treatment targets when on treatment, would be helpful. It is difficult to keep track of the differences between guidelines, particularly for readers not familiar with the topic. This does not require the same level of detail as that in the supplement. It could also be combined with Tables 2 and 3. 3. Results p9, line 55-56: this is no longer strictly true following the publication of the ISH 2020 guideline. 4. Results p12, ESC/ESH 2018 guidelines: it should be acknowledged here that those with high-normal (130-139/85-89) may be considered for treatment if cardiovascular risk is very high. I agree treatment goals are not precisely defined, but the guidelines do state that BP targets <130/80 mmHg should be targeted 'in most patients' – with a stronger recommendation for this in those <65. I would suggest calculating, as a sensitivity analysis the threshold of <65s meeting the lower threshold and presenting both here. 5. Results, p14 first sentence: 'participants with an…compared with participants without' – as a comparison is stated in the sentence, a p-value should be given. It would appear from the 95% Cis that there is no statistically significant difference between the two groups, in which case the text is somewhat misleading here – in the figure, the CV risk is higher for those on medication in all guidelines. However, from the supplementary tables S5-9, p-values are given, which don't appear to match up to the confidence intervals presented. Can the authors clarify the discrepancy here? I also think interpretation has relied too much on a binary split at p=0.05 – the p-values for ESC/ESH 2018 and JNC are similar. 6. Discussion: final paragraph: SPRINT and HOPE-3 have had major impacts on hypertension guidelines, with the former influencing the AHA guidelines, so worth mentioning in discussion – and both published more recently than the meta-analysis presented. 7. Discussion: limitations of the study, including local context, data limitations and generalisability are not discussed. 8. Discussion: The authors have nicely presented the differences in the guidelines, and shown to an extent how ACC/AHA may be more discrimatory, but the key unaddressed question is why these discrepancies in guidelines exist. The article concludes that further RCTs are needed, but is the key implication here not why guidelines themselves differ? Particularly in the case of ACC/AHA and ESC/ESH, guideline authors have presumable had access to the same evidence-base, yet recommendations are very different. 'Conclusive' evidence might lead to guidelines adopting the same recommendations, but there will always be differences in interpretation and questions over the applicability to different

	contexts. I would like to see some deeper discussion on the differences in guidelines as this will contextualise the findings. 9. Another major guideline, ISH 2020 was published this year and the authors may wish to consider including this in the analysis given the applicability of the ISH guidelines to lower income countries.

REVIEWER	Laurent Billot The George Institute for Global Health, Australia
REVIEW RETURNED	21-Oct-2020

GENERAL COMMENTS	My main concern lies with the fact that the analyses are observational and subject to confounding. When comparing event rates between those "recommended vs not recommended" I would encourage the authors to perform additional analyses adjusted for other cardiovascular risk factors (e.g. lipid levels) which are not included in the hypertension recommendations. In the strength and weakness section as well as in the discussion, I would suggest adding a statement about the fact that it is an observational study and that associations between recommendations and cardiovascular events could potentially be confounded by other (cardiovascular risk) factors. Please consider including a consort diagram indicating the number of participants included at baseline, at the 5 year follow-up and the 10-year follow-up. Is it possible to check the proportions under each recommendation during follow-up or is the necessary information only available at baseline? If only 8 out of 1699 participants not taking antihypertensive medication at baseline were missing BP data please consider removing the following sentence: "Participants with missing BP data did not significantly differ from those with BP data (data not shown)." (cf lines 3-6 on Page 8) since differences are unlikely to be significant with such a small sample size and the proportion missing is negligible. In their current forms, Table 2 and Table 3 include a lot white space. I would suggest combining them both and removing some of the text in column 1. I would further suggest using a forest plot instead a table. The forest plot would show the estimated proportion and confidence interval according to each guideline (rows) with one panel/column for the proportion not on treatment who should be and another panel/column for the proportion on treatment but not reaching target. I would encourage the authors to try and reduce the number of supplementary tables as follows: - Please consider removing Table S1 which appears to repeat the information from Figures S1-S5. - Please consider adding a "Total" column to Table 1 with the characteristics of all 4814 participants instead of having a separate table (Table S2). - Instead of having 5 separate tables (tables S5-S9) comparing baseline characteristics between those with vs without a recommendation according to all 5 guidelines, please consider a single table focusing on the differences between the guidelines i.e.

	only including those for whom medication is recommended (excluding the 'no' columns). In doing so, I would not include p-values but try to point out where the guidelines lead to different population profiles especially with regards to co-morbidities.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1

Overall, this is a very well-written manuscript. It describes the rationale and key details pertaining to the scientific methodology of the study hypothesis well. The topic of the paper is also timely and fills gaps in research. While I have minimal concerns for its publication, the following are a few minor points for the authors to note:

1. Please examine the entire manuscript for typos, grammar, and sentence flow in general (e.g. "Methods" is spelled incorrectly in the abstract)

→Thank you, we now rechecked the manuscript.

2. On page 5, lines 38 to 43, it is not clear what "Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research" means, or what its significance is. If not pertinent, I suggest removing it. It is also repeated on page 6, lines 3-5.

→The author guidelines of BMJ Open require this patient and public involvement statement.

3. Page 7, line 21 – please use numbered superscript for in-text citation of SPSS software.

→Done.

4. Description of the respective guidelines should be in the methods section, not the results section.

→ We now added a hypertension guidelines chapter to the methods section, that the reader gets informed about the guidelines in detail before reading the results. However, we would like to include a summary of the most important suggestions of each guideline in close proximity to the result of this suggestion for the population, to keep the flow of reading and prevent scrolling/switching documents.

Reviewer #2

The authors of these analyses have used the data of treated and untreated subjects having participated in a German cohort to compare the impact of several hypertension guidelines including the recent ACC/AHA and the ESC/ESH guidelines. Their results show that the percentage of untreated patients who would have been treated according to the recent US guidelines would be higher and the percentage of patients achieving target BP under treatment would be lower when following the last US guidelines. The incidence of cardiovascular events is also higher according to these guidelines. The idea to compare the impact of the different guidelines on a population of treated and untreated hypertensive patients is interesting. However, this set of analysis raise up few questions.

1. The first is whether it is useful to analyse guidelines that are not recommended anymore. Why not concentrate on the most recent guidelines including the 2020 ISH guidelines that have now been published.

→We thank the reviewer for raising this important point of criticism. By the time we submitted this paper (beginning of March), the 2020 ISH guidelines were not published. We now included them into our paper.

2. The last ACC/AHA guidelines have changed the definition of hypertension and defined new categories at much lower levels of blood pressure. Hence, it is not surprising that there are more people to be treated and more patients with uncontrolled BP as they were not treated with this target in mind. This was already published by Muntner et al after the publication of ACC/AHA guidelines.

→The reviewer is right, the ACC/AHA guidelines define hypertension already at BP≥130/80 mmHg. Treatment with antihypertensive medication at BP 130-139/80-89 mmHg is however only recommended in case of high cardiovascular risk. As Muntner et al showed, the overall crude prevalence of hypertension based on the ACC/AHA guidelines among US adults was 45.6%, antihypertensive medication was recommended for 36.2%, and among those taking antihypertensive medication, 53.4% had BP above treatment goal. When these proportions were compared with the previously applied JNC7 guideline, Muntner et al could show that prevalence of hypertension and BP above treatment goal clearly increased with the application of the ACC/AHA guidelines, but proportions recommended for antihypertensive medication were similar.

We were actually inspired by the analyses of Muntner et al to compare the population impact of the ACC/AHA 2017 guideline on the American population with the population impact on the European, specifically German population. In Europe, there was a rather controversial discussion about the potential impact of the ACC/AHA 2017 guideline with some experts fearing a tremendous increase in medication prescription, rise in costs for the health system and possible side effects exceeding the beneficial effects of cardiovascular risk reduction. While Muntner et al showed no significant increase in new recommendations for pharmacological treatment for the American population, such data were missing for the European population. American study cohorts considerably differ from European cohorts in cardiovascular risk profile and treatment of cardiovascular risk factors because the European health care system, especially in primary care, uses less aggressive pharmacological treatment (e.g., McClelland et al. J Am Coll Cardiol. 2015;66(15):1643-53; Erbel Erbel et al. Eur Heart J. 2008;29:2782-91). Contrary to the results by Muntner et al, our results show a significant increase in new recommendations for pharmacological treatment for the German population when the ACC/AHA guidelines are applied compared with the JNC7 guidelines (45.8% vs 37.2%).

3. There is one missing issue regarding the ESC/ESH recommendations. In patients with a systolic BP between 130 and 139 and diastolic BP between 85 and 89, treatment is recommended if patients have a very high cardiovascular risk in particular patients with coronary heart disease and cerebrovascular disease. This does not appear in the paper.

→For the implementation of the different hypertension management guidelines in the HNR cohort, we only included at least IIa class of recommendations with at least B level of evidence, as stated in the methods section on page 7 of the paper. There is only a class IIb recommendation for treating very high risk patients with high-normal BP. In the ESC/ESH 2018 guidelines it is stated that “In a meta-analysis of 10 RCTs or RCT subgroups that also included individuals at high or very high cardiovascular risk, mostly with previous CVD and untreated high–normal and normal BP (n = 26 863), BP-lowering drug treatment, achieving an SBP reduction of 4 mmHg, reduced the risk of stroke but not any other cardiovascular events [217]. In another analysis of trials including people with previous CAD and a mean baseline SBP of 138 mmHg, treatment was associated with reduced risk for major cardiovascular events (relative risk 0.90; 95% confidence interval 0.84–0.97), but was not associated with an increased survival (relative risk 0.98; 95% confidence interval 0.89–1.07) [201]. Thus, the benefit for treating people with high–normal BP appears marginal and, if present, appears to be restricted to those at very high cardiovascular risk and established CVD, especially CAD.” (page

1977) “BP-lowering drugs **may be considered** for patients with high–normal BP and established CVD, especially CAD.” (page 1978)

Initiation of hypertension treatment according to office BP

Recommendations	Class[a]	Level[b]
Prompt initiation of BP-lowering drug treatment is recommended in patients with grade 2 or 3 hypertension at any level of CV risk, simultaneous with the initiation of lifestyle changes [2,8].	I	A
In patients with grade 1 hypertension: • Lifestyle interventions are recommended to determine if this will normalize BP [219].	II	B
• In patients with grade 1 hypertension at low–moderate-risk and without evidence of HMOD, BP-lowering drug treatment is recommended if the patient remains hypertensive after a period of lifestyle intervention[c] [211,212].	I	A
• In patients with grade 1 hypertension and at high risk or with evidence of HMOD, prompt initiation of drug treatment is recommended simultaneously with lifestyle interventions [211,212].	I	A
In fit older patients with hypertension (even if aged > 80 years), BP-lowering drug treatment and lifestyle intervention are recommended when SBP is ≥ 160 mmHg [210,220,221].	I	A
BP-lowering drug treatment and lifestyle intervention are recommended for fit older patients (> 65 years but not > 80 years) when SBP is in the grade 1 range (140–159 mmHg), provided that treatment is well tolerated [212].	I	A
Antihypertensive treatment may also be considered in frail older patients if tolerated [215].	IIb	B
Withdrawal of BP-lowering drug treatment on the basis of age, even when patients attain an age of ≥ 80 years, is not recommended, provided that treatment is well tolerated [213].	III	A
In patients with high–normal BP (130–139/85–89 mmHg): • Lifestyle changes are recommended [17,35].	I	A
• Drug treatment may be considered when their cardiovascular risk is very high due to established CVD, especially CAD [217].	IIb	A

Considering participants with a systolic BP between 130 and 139 and diastolic BP between 85 and 89 with a history of stroke or CAD (n=16) for antihypertensive medication recommendation, does not change our results to a relevant extent and is thus not shown in the paper.

4. When comparing the different guidelines in Figure 1, it appears that in age and sex-corrected analyses there are no difference between ESC/ESH and ACC/AHA impact on 5-year cardiovascular events. This should be discussed. Indeed, in the end the difference between the two guidelines are minor because not all patients with an elevated BP according to ACC/AHA guidelines should be treated with drugs.

→The reviewer is completely right, the age-and sex-adjusted incidence rates showed that even though the difference between participants with and without antihypertensive medication recommendation is largest for ACC/AHA (0.5%), it only marginally differs from ESH/ESC 2013 (0.4%). Thus, the discriminatory value of ACC/AHA is considerably based on non-modifiable risk factors since ACC/AHA recommends treatment at lower BP levels in elderly people. We now stressed this observation on page 14 and page 16.

5. The incidence of CV events is greater when using the ACC/AHA guidelines. This is not surprising as the number of patients concerned is greater and it is well known that cardiovascular events occurs although in patients with optimal, normal and high normal BP. The incidence rate is about 1% per year (Vasan et al, NEJM, 2001). Thus, these analyses are not really surprising.

→That is an important point that needs to be considered. We now stressed this point in our discussion on page 16.

Minor comments:

On page 40/44, the value of diastolic BP in the no column should be corrected:

77 instead of 777

→Thank you, this was a typo, we now corrected it and rechecked our tables for typos.

Reviewer #3

This is an interesting paper which addresses an important and under-researched topic. Gronewold et al demonstrate significant differences that exist between hypertension guidelines based on the criteria for diagnosis. They base these findings not only on the BP threshold, but also on the characteristics of underlying cardiovascular risk. Given the wide use of hypertension guidelines around the world, this article is a welcome addition to the literature. As I mention below, I would like to see more in-depth discussion of the impact of the findings.

In terms of statistical analyses, these are mostly well-described and appropriate, but I have one comment below. Missing data has been presented clearly, and on the whole is minimal. In the case of CIMT values, where missing data could have an impact, a sensitivity analysis has been carried out

I have a few other comments and suggestions:

1. Methods p6: further description of the study cohort is required in the paper regarding the method of BP measurement (this information is currently in the appendix), but is key to interpretation, particularly given the move towards ambulatory monitoring of BP in recent guidelines.

→We now provide BP measurement as well as assessment of antihypertensive medication, which are key to the interpretation of our results, in the methods section on page 5.

2. Results: a summary table of the thresholds and indication for initiating treatment, and for treatment targets when on treatment, would be helpful. It is difficult to keep track of the differences between guidelines, particularly for readers not familiar with the topic. This does not require the same level of detail as that in the supplement. It could also be combined with Tables 2 and 3.

→We now combined thresholds for initiating treatment with Table 2 and treatment targets with Table 3.

3. Results p9, line 55-56: this is no longer strictly true following the publication of the ISH 2020 guideline.

→That is right, be the time we submitted the present paper (beginning of March 2020), the ISH 2020 guideline has not been published. To offer an up-to-date overview of hypertension guidelines, we now included the recent ISH 2020 guideline in our paper.

4. Results p12, ESC/ESH 2018 guidelines: it should be acknowledged here that those with high-normal (130-139/85-89) may be considered for treatment if cardiovascular risk is very high.

→ For the implementation of the different hypertension management guidelines in the HNR cohort, we only included at least IIa class of recommendations with at least B level of evidence, as stated in the methods section on page 7 of the paper. Treating high-normal BP in very high cardiovascular risk only got a IIb class of recommendation. When we consider participants with a systolic BP between 130 and 139 and diastolic between 85 and 89 with a history of stroke or CAD (n=16) for antihypertensive medication recommendation, this does not change our results to a relevant extent.

I agree treatment goals are not precisely defined, but the guidelines do state that BP targets <130/80 mmHg should be targeted 'in most patients' – with a stronger recommendation for this in those <65. I would suggest calculating, as a sensitivity analysis the threshold of <65s meeting the lower threshold and presenting both here.

→We now calculated a sensitivity analysis with a treatment goal of SBP <130 mmHg and DBP <80 mmHg in all persons <65 years and a treatment goal of SBP <140 mmHg and DBP <90 mmHg in all persons ≥65 years as suggested and present the results on page 12.

5. Results, p14 first sentence: 'participants with an…compared with participants without' – as a comparison is stated in the sentence, a p-value should be given. It would appear from the 95% CIs that there is no statistically significant difference between the two groups, in which case the text is somewhat misleading here – in the figure, the CV risk is higher for those on medication in all guidelines. However, from the supplementary tables S5-9, p-values are given, which don't appear to match up to the confidence intervals presented. Can the authors clarify the discrepancy here? I also think interpretation has relied too much on a binary split at p=0.05 – the p-values for ESC/ESH 2018 and JNC are similar.

→Yes, thank you for notifying, there is a discrepancy because we used exact methods for confidence interval calculation (Clopper-Pearson two-sided 95% binomial confidence intervals, https://statpages.info/confint.html) and asymptotic methods for p-value calculation (asymptotic two-sided Pearson chi-square test). We now corrected this mistake and used exact significance testing.

6. Discussion: final paragraph: SPRINT and HOPE-3 have had major impacts on hypertension guidelines, with the former influencing the AHA guidelines, so worth mentioning in discussion – and both published more recently than the meta-analysis presented.

→We now extended our discussion section and discussed the influence of the SPRINT and HOPE-3 trial on hypertension guidelines on page 19-21.

7. Discussion: limitations of the study, including local context, data limitations and generalisability are not discussed.

→We now included a "strengths and limitations of the study" section in the discussion including local context, data limitations and generalisability.

8. Discussion: The authors have nicely presented the differences in the guidelines, and shown to an extent how ACC/AHA may be more discriminatory, but the key unaddressed question is why these discrepancies in guidelines exist. The article concludes that further RCTs are needed, but is the key implication here not why guidelines themselves differ? Particularly in the case of ACC/AHA and ESC/ESH, guideline authors have presumable had access to the same evidence-base, yet recommendations are very different. 'Conclusive' evidence might lead to guidelines adopting the same recommendations, but there will always be differences in interpretation and questions over the applicability to different contexts. I would like to see some deeper discussion on the differences in guidelines as this will contextualise the findings.

→We now provide an in-depth discussion about possible reasons for the discrepancies in guidelines, especially for the current ACC/AHA and ESC/ESH guidelines including development process and underlying evidence (page 16-22).

9. Another major guideline, ISH 2020 was published this year and the authors may wish to consider including this in the analysis given the applicability of the ISH guidelines to lower income countries.

→Unfortunately, this guideline has not been published when we submitted our paper. We now included ISH 2020 to provide an up-to-date overview about hypertension guidelines and their population impact.

Reviewer #4

My main concern lies with the fact that the analyses are observational and subject to confounding. When comparing event rates between those "recommended vs not recommended" I would encourage the authors to perform additional analyses adjusted for other cardiovascular risk factors (e.g. lipid levels) which are not included in the hypertension recommendations.

→The reviewer is right, our analyses in the present paper are observational and shall not be interpreted in a causal way. In previous papers where we intended causal inference (e.g. Gronewold et al. Hypertension. 2019;74:1436-1447; Knispel et al. J Immunother Cancer. 2020;8:e000395) we used state-of-the-art methods to control confounding like directed acyclic graphs (DAGs) to identify adjustment variables or inverse probability treatment weighting (IPTW) to balance confounders. The overarching goal of the present paper is to increase critical knowledge about hypertension guidelines to improve BP control and prevent its negative consequences. Similar to the previous analysis by Muntner et al, who showed the differences between the new and the previous American hypertension guideline and compared their impact on the American population, we wanted to show the impact on the European (German) population. We did not adjust for further cardiovascular risk factors since they are already included in the recommendations when to start antihypertensive treatment. Further, the hypertension guidelines do not aim at recommending treatment for other cardiovascular risk factors than BP. In order to draw causal inference about the efficacy of implementing the recommendations of the different hypertension guidelines, RCTs which randomize people to the different guideline recommendations would be needed as gold standard, which we now further emphasize in the "strengths and limitations of the study" section in the discussion.

In the strength and weakness section as well as in the discussion, I would suggest adding a statement about the fact that it is an observational study and that associations between recommendations and cardiovascular events could potentially be confounded by other (cardiovascular risk) factors.

→We now included this limitation of observational studies in the "strengths and limitations of the study" section in the discussion.

Please consider including a consort diagram indicating the number of participants included at baseline, at the 5 year follow-up and the 10-year follow-up.

→We included only baseline data regarding blood pressure, antihypertensive medication, and cardiovascular risk factors. Missing values at baseline are shown in Supplemental Table 1. Incident cardiovascular events were assessed in annual questionnaires and validated by an independent endpoint committee. We only included incident cardiovascular events occurring between baseline and 5-year follow-up because some study variables were disclosed to study participants at the 5-year follow-up which changes treatment patterns and subsequent cardiovascular risk. Information about incident cardiovascular events occurring before the 5-year follow-up was available for the total study cohort, because the study personnel sent reminders in case questionnaires were not returned or even used telephone interviews. Consequently, we did not consider a consort diagram necessary for the present study.

Is it possible to check the proportions under each recommendation during follow-up or is the necessary information only available at baseline?

→Yes, blood pressure, antihypertensive medication, and cardiovascular risk factors were also assessed at the 5-year-follow-up and at the 10-year-follow-up. However, as explained above, some study variables were disclosed to study participants at the 5-year-follow-up which changes treatment patterns and subsequent cardiovascular risk. Further, there might be systematic loss to follow-up. While 86% of the total cohort took part in the 5-year follow-up, these were only 64% at the 10-year-follow-up.

If only 8 out of 1699 participants not taking antihypertensive medication at baseline were missing BP data please consider removing the following sentence: "Participants with missing BP data did not significantly differ from those with BP data (data not shown)." (cf lines 3-6 on Page 8) since differences are unlikely to be significant with such a small sample size and the proportion missing is negligible.

→We deleted this sentence.

In their current forms, Table 2 and Table 3 include a lot white space. I would suggest combining them both and removing some of the text in column 1. I would further suggest

using a forest plot instead a table. The forest plot would show the estimated proportion and confidence interval according to each guideline (rows) with one panel/column for the proportion not on treatment who should be and another panel/column for the proportion on treatment but not reaching target.

→Based on the suggestion of Reviewer 3 to include a summary of the thresholds and indication for initiating treatment, and for treatment targets when on treatment in Table 2 and Table 3, because it is difficult to keep track of the differences between guidelines, we combined thresholds for initiating treatment with Table 2 and treatment targets with Table 3. The tables have less white space now and the guidelines are shown in rows instead of columns, which matches your idea of using a forest plot.

I would encourage the authors to try and reduce the number of supplementary tables as follows:

- Please consider removing Table S1 which appears to repeat the information from Figures S1-S5.

→We removed Table S1.

- Please consider adding a "Total" column to Table 1 with the characteristics of all 4814 participants instead of having a separate table (Table S2).

→Baseline characteristics of the total Heinz Nixdorf Recall study cohort are already presented in an extremely high number of publications and are not of high relevance for the present paper. Further, it is now recommended to show missing data, thus we would have to include two additional columns in Table 1 which distract the reader from the most important information.

- Instead of having 5 separate tables (tables S5-S9) comparing baseline characteristics between those with vs without a recommendation according to all 5 guidelines, please consider a single table focusing on the differences between the guidelines i.e. only including those for whom medication is recommended (excluding the 'no' columns). In doing so, I would not include p-values but try to point out where the guidelines lead to different population profiles especially with regards to co-morbidities.

→We agree that the Supplement is rather detailed. However, the information in the Supplement is not published together with the main manuscript, thus people who are not interested in these information do not have to download and read the Supplement. Since we now also included the recently published ISH 2020 guideline, we would need a 7 columns x 37 lines Table, which gets hard to read. By just including those for whom medication is recommended in one table, information gets incomplete and additionally we cannot use our bold formatting to highlight the variables which are included in each guideline.

VERSION 2 – REVIEW

REVIEWER	Thomas Beaney Imperial College London, UK
REVIEW RETURNED	24-Dec-2020

GENERAL COMMENTS	Thank you to the authors for addressing/clarifying all my comments, and now including the latest ISH guidelines in addition. I welcome the discussion of reasons for differences between guidelines added to Discussion, but this could be summarised more concisely. A brief discussion of HOPE and SPRINT, for example, would suffice, and the reader can find this information if interested.

REVIEWER	Laurent Billot

	The George Institute for Global Health, Faculty of Medicine, UNSW Sydney, Australia
REVIEW RETURNED	21-Dec-2020

GENERAL COMMENTS	My earlier comments have been adequately addressed. I have no further comment.