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Reviewer A

Comment 1: Seems that subjects enrolled in the trial hadn't a severe hypertension (HTN) and an optimal BP control wasn't pursued (line 127) so 36.5 % of participants (Q3 & Q4) didn't reach SBP 140 mmHg target. Moreover, only enalapril 10 mg, nitrendipine 10 mg BID and 25 mg HCTZ was therapy at the maximum, seems not a big deal of therapy, taking into account the dose of ACE-inhibitor and the low strength of nitrendipine as chosen CCB.

The association between non optimal control of DBP -mainly- and UA rising level overtime is an interesting one.

Nitrendipine is preferred to HCTZ as combined anti-HTN medication, however it would be useful a sub-group analysis to try to clarify the known UA increasing impact of this thiazide diuretic overtime.

Replay 1:

Thanks for your comment.

As suggested, we have reported in the Results section of the revised manuscript as follows:

None of the other variables, including diuretics usage during the treatment period (no *vs.* yes) significantly modified the association between time-averaged on-treatment DBP (median, <82.9 *vs.* ≥82.9mmHg) and the risk of new-onset hyperuricemia (All *P*-interactions >0.05). (See page13, line 285-288)

Comment 2: Abstract background item: there is written the aim of the study and not properly a background i.e. why HTN and UA are analyzed and studied together.

Replay 2:

As suggested, we have supplemented the background as follows:

The relationship of blood pressure (BP) control with the risk of new-onset hyperuricemia remains uncertain. (See page 3, line 38-39)

Comment 3: CI is a range so is a tradition to write it down with a minus sign and not a comma to separate the extremes of the range.

Replay 3:

As suggested, we have revised the comma as a minus sign to separate the range in the revised manuscript.

Comment 4: Line 122: CI 0.98-1.40 shows non significance of the relationship between hyperuricemia and DBP in the range 85-90 mmHg: in the description is written in a way that seems a significant one relationship.

Replay 4:

As suggested, we have updated the revised manuscript as follows:

Consistently, when modeled as clinical categories, compared with participants with time-averaged on-treatment DBP <85mmHg, the adjusted odds ratios (95%CI) for participants with time-averaged DBP 85-<90, and ≥90mmHg were 1.16 (95%CI: 0.99-1.34) and 1.33 (95%CI: 1.11-1.59) (*P* for trend=0.001), respectively. Accordingly, a significantly higher risk of new-onset hyperuricemia was observed in participants with time-averaged DBP ≥85 mmHg (OR, 1.21; 95%CI: 1.06-1.39), compared with those with time-averaged DBP <85mmHg (Supplemental Table 4). (See page 11, line 235-241)

Comment 5: Line 358: "could" would be more appropriate than "would" in respect to guidelines first because HTN is more important than UA in CV risk assessment because UA didn't enter Framingham CV risk factors, second because UA didn't enter the definition of metabolic syndrome.

Replay 5:

As suggested, we have revised the sentence as "These findings could have important implications for clinical practice and guidelines". (See page 18, line 396-397)

Reviewer B

I would congratulate the authors for this interesting paper, on the basis of their long-standing dedication to the better understanding and management of hypertension. In the current study, the authors have done a post-hoc analysis to the China Stroke Primary Prevention Trial (CSPPT) cohort, aiming to explore the degree of time-averaged on-treatment blood pressure (BP) control and new-onset hyperuricemia/uric acid (UA) in general hypertensive patients. Overall, the study was well-written but some major issues remain.

Several of my suggestions are as follows:

Comment 1: What's the relation between time-averaged on-treatment BP and maximum UA? Before you discretize the UA as hyperuricemia or not, it is necessary to do an analysis taking UA as a continuous variable as it is.

Replay 1:

As suggested, we have analyzed the relation of time-averaged on-treatment BP with UA at exit, and supplemented the results section of the revised manuscript as follows:

Similar results were found for change in serum UA concentrations (secondary outcome) (Figure 1B, Supplemental Table 3) and the exit UA concentrations

(Supplemental Figure 2). (See page 11, line 232-234)

Comment 2: Can you provide the Dose-Response Curves using cubic restricted spline analysis to demonstrate the relation between time-averaged on-treatment BP and UA change, maximum UA, respectively?

Replay 2:

As suggested, we have provided the dose-response curves using cubic restricted spline analysis to demonstrate the relation of time-averaged on-treatment BP with UA change, and exit UA levels, and supplemented the results section of the revised manuscript as follows:

Similar results were found for change in serum UA concentrations (secondary outcome) (Figure 1B, Supplemental Table 3) and the exit UA concentrations (Supplemental Figure 2). (See page 11, line 232-234)

Comment 3: How many patients were lost to follow up? How do you deal with them?

Replay 3:

Thanks for the comments. All the participants without uric acid measurements at the exit visit were excluded from the analysis.

As suggested, we have supplemented the results section as follows:

As illustrated in the flow chart (Supplemental Figure 1), of the 15,364 participants in the UA Sub-study of CSPPT, the final UA measurement at the exit visit was obtained for 13,163 (85.7%). Participants without UA concentrations at the exit visit did not differ substantially in baseline characteristics from those with UA concentrations (Supplemental Table 1). Of the 13,163 participants, a total of 10,617 subjects, who

did not use UA-lowing drugs during the treatment period, as well as whose baseline UA levels were <357μmol/L in the UA Sub-study of the CSPPT were included in the final analyses. (See page 10, line 205-212)

Comment 4: You have analyzed the association between time-averaged on- treatment BP and the risk of new-onset hyperuricemia by per SD increment. How about per 10 mmHg, which would be more clinically perceptible?

Replay 4:

As suggested, we have analyzed the association between time-averaged on- treatment BP and the risk of new-onset hyperuricemia by per 10 mmHg in all the related tables, and supplemented the results section as follows:

Overall, there was a significant positive association between time-averaged on-treatment DBP and the risk of new-onset hyperuricemia (per 10mmHg increment; OR, 1.13; 95%CI: 1.02–1.26) (Figure 1A, Table 2). (See page 11, line 226-228)

Comment 5: As you stated, hyperuricemia is not only a strong predictor of gout but is also associated with the risk of chronic kidney disease, stroke, cardiovascular diseases and mortality. Since this is a post-hoc study, it would be readily available for you to see the impact of UA on cardiac adverse events (e.g. mortality and stroke). And I think it essential for clinical counselling. Please provide the data.

Replay 5:

Thanks for the comments.

As suggested, we have supplemented the limitation section in the revised manuscript as follows:

Fourth, although the positive relation of UA levels with risk of stroke and mortality in

previous studies (8), our current study did not find the significant association between baseline UA and first stroke (Per SD increment; HR, 0.98, 95%CI:0.88-1.09) (Supplemental figure 7A). However, our study found a positive association between baseline UA and all-cause mortality (Per SD increment; HR, 1.15, 95%CI: 1.03-1.29) (Supplemental figure 7B). Therefore, the association between UA levels and cardiovascular diseases in treated hypertensive patients still should be further investigated in future studies. (See page 17, line 378-386)

Comment 6: Although you have tried to explain why there was no significant association between time-averaged on-treatment SBP and the primary or secondary outcomes, it seems not convincing at all. You might need to dig deeper into this intriguing phenomenon.

Replay 6:

Thanks for the comments. As suggested, we have supplemented the discussion section in the revised manuscript as follows:

While biological mechanisms underlying our observed BP control-new onset hyperuricemia association remain to be determined, our findings are biologically plausible. First, hypertension may result in renal vascular resistance accompanied by reduction in renal blood flow (28). As renal blood flow decreases, an increase in proximal sodium and UA absorption occurs, which may contribute to increasing serum UA levels (19,29,30). Second, microvascular damage associated with hypertension may result in local tissue ischemia (29). In ischemic conditions, adenosine triphosphate is degraded to adenine and xanthine, and the conversion of xanthine dehydrogenase to xanthine oxidase is simultaneously increased, which leads to increased UA production (30,34-36). Overall, renal microvascular damage and

intrarenal ischemia may contribute to the major explanation for the high, new-onset hyperuricemia burden in hypertensive patients.

However, our study found no significant association between time-averaged on-treatment SBP during the treatment period and hyperuricemia risk. The possible explanations included, first, elevated SBP is mainly associated with large artery stiffness, while DBP rises with increases in peripheral vascular resistance (37). As such, at a given sample size, DBP control may possibly have a greater effect on renal blood flow and change in UA levels, and therefore, we mainly observed the significant association between DBP control and new-onset hyperuricemia in our current study. Second, we really found a non-significant increased risk of new-onset hyperuricemia in participants with time-averaged on-treatment SBP ≥120mmHg (*vs.* <120mmHg; OR, 1.61; 95%CI: 0.88-2.97). Because only few participants (1.7%) reached a time-averaged on-treatment SBP goal of <120mmHg, these results may just indicate that our current study was underpowered for evaluating the relation of time-averaged SBP<120mmHg (*vs.* ≥120mmHg) with new-onset hyperuricemia. Of note, in the stratified analysis (Figure 2), the lowest new-onset hyperuricemia risk was found in those with both lower DBP and lower SBP levels. These results suggested that a relatively stricter both SBP and DBP control may lead to a greater reduction of new-onset hyperuricemia in general hypertensive patients. However, more studies are needed to verify our results and hypothesis. (See page 15-16, line 324-329, 334-340, 352-369)

Comment 7: The study demonstrated that a tight DBP control of <82.9mmHg was associated with a lower risk of new-onset hyperuricemia among treated hypertensive patients without hyperuricemia. I doubt the reliability of this conclusion. Yes, there is

a difference between the higher and lower DBP groups. However, the incidence of new-onset hyperuricemia in the lower DBP group is still very high (14.1%) compared to the higher one (17.3%). And the lower limit of 95% CI (1.01) almost missed its significant point (per SD increment; OR,1.09; 95%CI:1.01, 1.18). That is to say, a cutoff of 82.9mmHg of DBP would incur unacceptably high false negative rate and false positive rate due to its poor discrimination. A plausible solution, seems the only one, is to decrease the cutoff. 75, 70, 65 mmHg, etc.? Is it really applicable and beneficial to lower the DBP as much?

Replay 7:

Thanks for the comments.

Our study suggested that first, there was a significant positive association between time-averaged on-treatment DBP and the risk of new-onset hyperuricemia (per 10mmHg increment; OR,1.13; 95%CI:1.02–1.26) (Figure 1A, Table 2). Second, when time-averaged on-treatment DBP was assessed as quartiles, a significantly higher risk of new-onset hyperuricemia was found in participants with time-averaged on-treatment DBP ≥82.9mmHg (median) (*vs.* <82.9mmHg; OR, 1.25; 95%CI: 1.10-1.44) (Table 2). (See page 11, line 226-232)

Because only few participants reached a time-averaged DBP goal of <70mmHg, as suggested, we categorized the time-averaged DBP as <75, 75-<80, 80-<85, 85-<90, and ≥90mmHg. Compared with those with time-averaged DBP <75mmHg, the adjusted odds ratios (95%CI) for participants with time-averaged DBP 75-<80, 80-<85, 85-<90, and ≥90mmHg were 1.06 (95%CI: 0.84-1.32), 1.06 (95%CI: 0.85-1.34), 1.22 (95%CI: 0.96-1.56) and 1.41 (95%CI: 1.07-1.86) (*P* for trend=0.004), respectively (Supplemental table 4).

As suggested, we have supplemented the results section as follows:

Consistently, when modeled as clinical categories, compared with participants with time-averaged on-treatment DBP <85mmHg, the adjusted odds ratios (95%CI) for participants with time-averaged DBP 85-<90, and ≥90mmHg were 1.16 (95%CI: 0.99-1.34) and 1.33 (95%CI: 1.11-1.59) (*P* for trend=0.001), respectively. Accordingly, a significantly higher risk of new-onset hyperuricemia was observed in participants with time-averaged DBP ≥85 mmHg (OR, 1.21; 95%CI: 1.06-1.39), compared with those with time-averaged DBP <85mmHg (Supplemental Table 4). (See page 11, line 235-241)

We have supplemented the discussion section as follows:

Of note, Figure 1 showed that the relation of time-averaged DBP with new-onset hyperuricemia seemed to be "S" shaped. That is to say, the beneficial effect of BP reduction on new-onset hyperuricemia may reach a plateau in those with relatively optimal BP levels. (See page 15-16, line 342-345)

At the same time, we have supplemented the limitation as follows:

Fifth, our study mainly suggested that a tight BP control was associated with lower risk of new-onset hyperuricemia. However, our study was underpowered to detect the optimal BP levels for new-onset hyperuricemia. (See page 17, line 386-388)

Comment 8: In Figure 1 the relationship of time-averaged on-treatment diastolic blood pressure (DBP) with new-onset hyperuricemia (A) and change in uric acid concentrations (B) are "S" shaped. Why a plateau should occur when DBP increases to a certain point? Isn't it true that the higher the DBP, the higher the risk of

hyperuricemia according to your discussion (renal microvascular damage and intrarenal ischemia theory)?

Replay 8:

As suggested, we have supplemented the discussion section as follows:

Of note, Figure 1 showed that the relation of time-averaged DBP with new-onset hyperuricemia seemed to be "S" shaped. That is to say, the beneficial effect of BP reduction on new-onset hyperuricemia may reach a plateau in those with relatively optimal BP levels. On the other hand, we speculated that when there has already been a relatively serious renal microvascular damage associated with high BP, the impaired renal blood flow and intrarenal ischemia could not continuously increase with the further increment of BP, and, therefore, there may be a plateau, but not a continuously increased new-onset hyperuricemia risk. Future studies are warrened to further examine the findings and the underlying mechanisms of BP control on the risk of hyperuricemia. (See page 15-16, line 342-351)

Reviewer C

This manuscript aimed to examine the association between degree of time-averaged on-treatment blood pressure (BP) control and new-onset hyperuricemia in general hypertensive patients，the advices are as follow:

Comment 1: The DBP control may have a greater effect on renal blood flow and change in UA levels, what is the mechanism?

Replay 1:

Thanks for the comments. As suggested, we have supplemented the discussion section as follows:

While biological mechanisms underlying our observed BP control-new onset

hyperuricemia association remain to be determined, our findings are biologically plausible. First, hypertension may result in renal vascular resistance accompanied by reduction in renal blood flow (28). As renal blood flow decreases, an increase in proximal sodium and UA absorption occurs, which may contribute to increasing serum UA levels (19,29,30). Second, microvascular damage associated with hypertension may result in local tissue ischemia (29). In ischemic conditions, adenosine triphosphate is degraded to adenine and xanthine, and the conversion of xanthine dehydrogenase to xanthine oxidase is simultaneously increased, which leads to increased UA production (30,34-36). Overall, renal microvascular damage and intrarenal ischemia may contribute to the major explanation for the high, new-onset hyperuricemia burden in hypertensive patients.

However, our study found no significant association between time-averaged on-treatment SBP during the treatment period and hyperuricemia risk. The possible explanations included, first, elevated SBP is mainly associated with large artery stiffness, while DBP rises with increases in peripheral vascular resistance (37). As such, at a given sample size, DBP control may possibly have a greater effect on renal blood flow and change in UA levels, and therefore, we mainly observed the significant association between DBP control and new-onset hyperuricemia in our current study. Second, we really found a non-significant increased risk of new-onset hyperuricemia in participants with time-averaged on-treatment SBP ≥120mmHg (*vs.* <120mmHg; OR, 1.61; 95%CI: 0.88-2.97). Because only few participants (1.7%) reached a time-averaged on-treatment SBP goal of <120mmHg, these results may just indicate that our current study was underpowered for evaluating the relation of time-averaged SBP<120mmHg (*vs.* ≥120mmHg) with new-onset hyperuricemia. Of note, in the stratified analysis (Figure 2), the lowest new-onset hyperuricemia risk was

found in those with both lower DBP and lower SBP levels. These results suggested that a relatively stricter both SBP and DBP control may lead to a greater reduction of new-onset hyperuricemia in general hypertensive patients. However, more studies are needed to verify our results and hypothesis. (See page 15-16, line 324-329, 334-340, 352-369)

Comment 2: In discussion, the study found no significant association between SBP and hyperuricemia risk, a non-significant increased risk of new-onset hyperuricemia in participants with time-averaged on-treatment SBP≥120mmHg, but then the lowest new-onset hyperuricemia risk (12.1%) was found in those with both lower DBP and lower SBP levels, why ? the author should provide a better explanation

Replay 2:

Thanks for the comments. We speculated that our current study was underpowered for evaluating the relation of time-averaged SBP with new-onset hyperuricemia. However, we could not conclude that SBP had no effect on new-onset hyperuricemia.

As suggested, we have supplemented the discussion section as follows:

However, our study found no significant association between time-averaged on-treatment SBP during the treatment period and hyperuricemia risk. The possible explanations included, first, elevated SBP is mainly associated with large artery stiffness, while DBP rises with increases in peripheral vascular resistance (37). As such, at a given sample size, DBP control may possibly have a greater effect on renal blood flow and change in UA levels, and therefore we mainly observed the significant association between DBP control and new-onset hyperuricemia in our current study. Second, we really found a non-significant increased risk of new-onset hyperuricemia in participants with time-averaged on-treatment SBP ≥120mmHg (*vs.* <120mmHg;

OR, 1.61; 95%CI: 0.88-2.97). Because only few participants (1.7%) reached a time-averaged on-treatment SBP goal of <120mmHg, these results may just indicate that our current study was underpowered for evaluating the relation of time-averaged SBP<120mmHg (*vs.* ≥120mmHg) with new-onset hyperuricemia. Of note, in the stratified analysis (Figure 2), the lowest new-onset hyperuricemia risk was found in those with both lower DBP and lower SBP levels. These results suggested that a relatively stricter both SBP and DBP control may lead to a greater reduction of new-onset hyperuricemia in general hypertensive patients. However, more studies are needed to verify our results and hypothesis. (See page 16, line 352-369)

Comment 3: More evidences and references from basic and clinical studies are needed to support the mechanism of the relationship between uric acid and blood pressure

Replay 3:

Thanks for the comments. As suggested, we have supplemented more references to support the mechanism of the relationship between uric acid and blood pressure, as updated the discussion section as follows:

While biological mechanisms underlying our observed BP control-new onset hyperuricemia association remain to be determined, our findings are biologically plausible. First, hypertension may result in renal vascular resistance accompanied by reduction in renal blood flow (28). As renal blood flow decreases, an increase in proximal sodium and UA absorption occurs, which may contribute to increasing serum UA levels (19,29,30). Consistently, it has been reported that the administration of angiotensin II reduces renal urate clearance in combination with a significant decrease in renal blood flow (28,31-34). Furthermore, Messerli FH et al (18) reported

an inverse association between renal blood flow and UA levels, and a positive relation of renal vascular resistance with UA concentrations in a study on general hypertensive patients. Second, microvascular damage associated with hypertension may result in local tissue ischemia (29). In ischemic conditions, adenosine triphosphate is degraded to adenine and xanthine, and the conversion of xanthine dehydrogenase to xanthine oxidase is simultaneously increased, which leads to increased UA production (30,34-36). Overall, renal microvascular damage and intrarenal ischemia may contribute to the major explanation for the high, new-onset hyperuricemia burden in hypertensive patients. We speculate that BP control may decrease microvascular resistance or damage, improve renal blood flow and tissue ischemia, and therefore, reduce the risk of new-onset hyperuricemia. (See page 15, line 324-342)