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Controversy about COOPERATE ABPM Trial Data

To the Editor: I was going over the COOPERATE substudy data regarding the effects of the treatment regimens on office and ambulatory blood pressure (BP), published in *Am J Nephrol* 2004; 24:543–548. The data are presented in table 3 and it is difficult to internally reconcile the data sets. For all 3 groups and at all of the different follow-up time periods (6 months, 1, 2 and 3 years), the daytime ambulatory systolic BP is greater than the outpatient BP by 10–15 mm Hg. While this is unusual, the real problem is that it is difficult to see how one can have a 24-hour systolic BP which is only 1–3 mm Hg higher than the nighttime systolic BP when the daytime systolic BP is 10–15 mm Hg higher (for 16 of 24 h). In fact, for year 3, the nighttime systolic BP is stated to be 1 mm Hg higher than the 24-hour systolic BP for 2 of the 3 groups. It would be important to get an explanation, even at this late stage.

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In Response: The main issues questioned by the corresponding author are summarized as follows: (1) why were the daytime ambulatory BP values higher than the office BP values by 10–15 mm Hg, and (2) what is the reason for the relatively high values of the daytime ambulatory BP in comparison with the 24-hour systolic BP and the nighttime ambulatory BP values?

First question could be explained by the experimental design of the COOPERATE trial. The patients were requested to take their agents including interventional medications. Most patients received these drugs between 5 and 7 a.m., 5–4 h before their regular consultation. Moreover, on measuring the office BP, they took a 15-min rest in the supine position in quiet rooms. Our nurses measured the BPs four times within a 5-min interval. We discarded the highest and the lowest values. Therefore, the office BP values would be lower than the daytime BP values. The latter values were greatly influenced by the patients' daytime activities.

The second question can mainly be explained by two observational findings. First, as stated before, the daytime ambulatory BP values in our patients were greatly influenced by their daily activities. For example patient 134, allocated to the combination treatment group, had a daytime BP at 3 years of between 113/68 mm Hg in the office and 168/99 mm Hg during higher activity at work. Eighteen percent of his daytime systolic BPs were below 120

mm Hg, 63% between 120 and 150 mm Hg, and the remaining 19% more than 150 mm Hg. A similar incidence was observed among treatment groups. Interestingly, the high variability of the systolic BP values was more characteristic among patients who were able to effectively restrict their salt intake. As compared with the systolic values, the nighttime values were constant throughout the measurements, partly because the drugs were taken at night or bedtime.

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To the Editor: I am afraid that the explanation provided by Dr. Nakao does not address the major discrepancy in the reported ambulatory BP data, but rather only the issue of the somewhat unusual finding of ~15 mm Hg higher daytime ambulatory systolic BP values as compared to the office systolic BP values. The primary discrepancy of concern is the fact that the 24-hour mean systolic BP values reported during the follow-up period are only 1–3 mm Hg higher than the mean nighttime systolic BP values and even lower by 1 mm Hg at 3 years when the daytime mean ambulatory systolic BPs are uniformly ~10–15 mm Hg higher. To illustrate, the losartan and trandolapril groups at 3 years had a daytime ambulatory mean systolic BP of 137 ± 12 and 138 ± 12 mm Hg and a nighttime systolic BP of 123 ± 11 and 124 ± 13 mm Hg, respectively, yet the 24-hour mean systolic BPs for the 2 groups are reported as 122 and 123 mm Hg; a physical impossibility. It is not clear how the specific data reported for patient 134 by Dr. Nakao addresses this issue, although it may explain the higher ambulatory daytime systolic BP as compared to the office systolic BP (113/68 mm Hg).

Curiously, there are some other discrepancies between the BP measurement protocols described in the present letter as compared to that reported previously in the two published manuscripts. In the parent study reported in *Lancet*, it was stated that the office BP was measured in the supine position by trained nurses after a bed rest of 15 min, *before* taking the trial drugs. The present letter states that the office BP was measured 4–5 h *after* taking the antihypertensive medications (between 5 and 7 a.m.). Additionally, both the *Lancet* report and the present letter states that the BP was obtained in the supine position, while the substudy reporting the ambulatory BP measurement data in the *American Journal of Nephrology* states that the office BP was measured in the sitting position as the mean of two consecutive readings (not 4 times with only the middle two readings being used as stated in the present letter). How can this be explained?

Anil Bidani

In Response: Thank you very much for your further comments. Initially, I have to say I am sorry for my misunderstanding of your initial letter.

It is quite reasonable for you to question the peculiar discrepancy regarding the mean ambulatory BP, the daytime BP and the nighttime BP measurements, especially at 3 years on each monotherapy. Therefore I have completely reviewed the medical records and the real data regarding the ambulatory BP measurements and found several problems in them. The details of my inquiry and the corrections are as follows.

First, the most serious error, with regard to the higher daytime and nighttime BP values compared with the mean 24-hour BP values, especially those reported at 3 years for the losartan and trandolapril patients. A similar error was found at 6 months among the trandolapril and combination groups, at 12 months

among the trandolapril and combination patients and, as the associate editor commented, at 36 months in patients on each monotherapy. Indeed this is impossible, and your comments are quite right. There is no excuse for such a discrepancy. Something was wrong in data management. Therefore, I have asked an independent nephrologist (Dr. T. Hasegawa) and a cardiologist (Dr. S. Mikami), who both work at the Khonan Hospital and are not connected in any way to the COOPERATE trial, to review all the ambulatory BP data. An Excel worksheet was used to develop table 3, and the table 3 posted in the *American Journal of Nephrology*. Surprisingly to us, and I apologize to the readers of the *American Journal of Nephrology* and to you, they found mismanagement of the data in the Excel worksheet. Assistants working for the COOPERATE-ABP substudy had made several mistakes by inserting part of the data into the Excel program. Therefore, after

Table 1

	Baseline			Month 6		
	losartan (n = 30)	trandolapril (n = 31)	combination (n = 31)	losartan (n = 30)	trandolapril (n = 31)	combination (n = 31)
Systolic OBP, mm Hg	137 ± 11	139 ± 13	137 ± 10	128 ± 8	128 ± 8	127 ± 9
Diastolic OBP, mm Hg	79 ± 7	80 ± 9	82 ± 8	75 ± 5	73 ± 5	76 ± 7
24-hour SBP, mm Hg	134 ± 11	134 ± 10	133 ± 10	128 ± 12	127 ± 12	126 ± 13
Day SBP, mm Hg	143 ± 12	144 ± 11	144 ± 12	133 ± 18	134 ± 15	133 ± 12
Night SBP, mm Hg	129 ± 9	130 ± 10	129 ± 10	123 ± 11	122 ± 12	123 ± 6
24-hour DBP, mm Hg	74 ± 7	73 ± 9	75 ± 9	71 ± 7	70 ± 8	71 ± 8
Day DBP, mm Hg	81 ± 9	83 ± 10	82 ± 9	79 ± 9	79 ± 8	79 ± 10
Night DBP, mm Hg	79 ± 6	80 ± 9	79 ± 9	72 ± 5	72 ± 7	73 ± 8
Day MAP, mm Hg	102	102	102	97	97	97
Night MAP, mm Hg	96	96	96	89	89	89
Night/day ratio of ABPM MAP	0.94	0.94	0.94	0.92	0.92	0.92

OBP = Office blood pressure; SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP = mean arterial pressure; ABPM = ambulatory blood pressure measurement

Table 2

	Baseline			Month 6		
	losartan (n = 30)	trandolapril (n = 31)	combination (n = 31)	losartan (n = 30)	trandolapril (n = 31)	combination (n = 31)
Systolic OBP, mm Hg	137 ± 11	139 ± 13	137 ± 10	128 ± 8	128 ± 8	127 ± 9
Diastolic OBP, mm Hg	79 ± 7	80 ± 9	82 ± 8	75 ± 5	73 ± 5	76 ± 7
24-hour SBP, mm Hg	134 ± 11	134 ± 10	133 ± 10	128 ± 12	127 ± 12	126 ± 13
Day SBP, mm Hg	143 ± 12	144 ± 11	144 ± 12	133 ± 18	134 ± 15	133 ± 12
Night SBP, mm Hg	129 ± 9	130 ± 10	129 ± 10	123 ± 11	122 ± 12	123 ± 6
24-hour DBP, mm Hg	79 ± 9	80 ± 8	79 ± 9	76 ± 8	76 ± 9	76 ± 10
Day DBP, mm Hg	84 ± 7	83 ± 9	83 ± 10	79 ± 8	78 ± 9	79 ± 9
Night DBP, mm Hg	77 ± 7	76 ± 9	76 ± 8	72 ± 5	72 ± 10	71 ± 8
Day MAP, mm Hg	84	83	83	79	78	79
Night MAP, mm Hg	77	76	76	72	72	71
Night/day ratio of ABPM MAP	0.92	0.92	0.92	0.91	0.92	0.90

consulting all my co-authors of the paper and obtaining their consent, I have decided to construct a new table 3, given here. Please note the corrected high-lightened values. A wide range of daytime systolic BP values was observed as compared with the nighttime systolic BP values, resulting in relatively high values for daytime systolic BP as stated in the previous letter. Office BP was depicted correctly without any changes as shown in table 3. Values used in figure 1 were correct so that no change was needed.

According to the new table 3, several lines in the Results section need correction:

p 545, right column, lines 30–31; 0.93 in the trandolapril group, and 0.93 in the combination group should be 0.94 in the trandolapril group, and 0.94 in the combination group

p 545, right column, line 33: 9/4 and 9/4 mm Hg should be 9/4 and 6/3 mm Hg

p 545, right column, line 34: p = 0.023 should be p = 0.45
p 545, right column, line 34: 10/4 mm Hg should be 7/4 mm Hg

p 545, right column, line 35: p = 0.001 should be p = 0.016
p 545, right column, line 37: p = 0.021 should be p = 0.042

p 545, right column, line 39: 0.21 for ABP should be 0.39 for ABP

p 546, line 1: 4/2 and 6/7 mm Hg should be 10/2 and 6/7 mm Hg

p 546, line 1: 4/4 should be 10/4
p 546, line 2: 6/8 mm Hg in the trandolapril group should be 8/8 mm Hg in the trandolapril group

p 546, line 2: 4/3 and 6/7 mm should be 11/3 and 6/6 mm

p 546, line 6: decreased to 0.90 should be decreased to 0.92

Year 1			Year 2			Year 3		
losartan (n = 30)	trandolapril (n = 31)	combination (n = 31)	losartan (n = 30)	trandolapril (n = 31)	combination (n = 31)	losartan (n = 30)	trandolapril (n = 31)	combination (n = 31)
125 ± 8	125 ± 11	126 ± 10	124 ± 9	123 ± 11	124 ± 8	124 ± 5	125 ± 6	124 ± 7
73 ± 5	71 ± 5	72 ± 7	72 ± 4	73 ± 5	73 ± 5	72 ± 7	73 ± 8	72 ± 9
129 ± 13	128 ± 10	126 ± 12	127 ± 13	125 ± 10	126 ± 12	126 ± 10	127 ± 12	126 ± 11
138 ± 11	132 ± 15	135 ± 13	131 ± 11	131 ± 11	133 ± 12	131 ± 13	132 ± 11	131 ± 13
121 ± 12	122 ± 11	120 ± 11	122 ± 11	122 ± 11	121 ± 10	122 ± 11	121 ± 13	122 ± 14
70 ± 6	70 ± 5	71 ± 8	69 ± 8	70 ± 7	71 ± 9	70 ± 8	71 ± 7	70 ± 8
77 ± 5	78 ± 7	77 ± 7	73 ± 8	73 ± 5	73 ± 6	72 ± 8	75 ± 8	72 ± 9
69 ± 9	70 ± 7	69 ± 9	67 ± 8	66 ± 9	64 ± 8	68 ± 7	68 ± 6	66 ± 5
97	96	96	92	92	94	92	94	92
86	87	87	85	85	83	86	87	84
0.89	0.91	0.90	0.92	0.92	0.89	0.94	0.92	0.92

Year 1			Year 2			Year 3		
losartan (n = 30)	trandolapril (n = 31)	combination (n = 31)	losartan (n = 30)	trandolapril (n = 31)	combination (n = 31)	losartan (n = 30)	trandolapril (n = 31)	combination (n = 31)
125 ± 8	125 ± 11	126 ± 10	124 ± 9	123 ± 11	124 ± 8	124 ± 5	125 ± 6	124 ± 7
73 ± 5	71 ± 5	72 ± 7	72 ± 4	73 ± 5	73 ± 5	72 ± 7	73 ± 8	72 ± 9
129 ± 13	128 ± 10	126 ± 12	127 ± 13	125 ± 10	126 ± 12	126 ± 10	127 ± 12	126 ± 11
138 ± 11	132 ± 15	135 ± 13	131 ± 11	131 ± 11	133 ± 12	131 ± 13	132 ± 11	131 ± 13
121 ± 12	122 ± 11	120 ± 11	122 ± 11	122 ± 11	121 ± 11	122 ± 11	121 ± 13	122 ± 14
73 ± 9	72 ± 5	72 ± 8	69 ± 8	70 ± 7	71 ± 10	70 ± 9	71 ± 10	70 ± 9
77 ± 11	78 ± 7	77 ± 9	73 ± 9	73 ± 8	73 ± 9	73 ± 5	75 ± 8	73 ± 10
69 ± 8	67 ± 8	68 ± 9	64 ± 9	65 ± 9	64 ± 9	64 ± 8	65 ± 7	64 ± 10
77	78	77	73	73	73	73	75	73
69	67	68	64	65	64	64	65	64
0.90	0.86	0.88	0.88	0.89	0.88	0.88	0.87	0.88

p 546, lines 9 and 10: p = 0.22 and 0.34 should be p = 0.24 and 0.32

p 546, line 11: p = 0.34 should be p = 0.41

p 546, line 12: p = 0.20 should be p = 0.22

p 547, left column, line 6: 0.56/0.39, 0.39/0.17, and 0.43/0.22, should be 0.48/0.30, 0.38/0.16, and 0.46/0.19

p 547, left column, lines 13–14: 0.98, 0.89–2.01, p = 0.17 should be 0.91, 0.80–1.99, p = 0.21

Second, with regard to the method of measuring office BP: it is my fault that on p 544 it is stated that ‘OBP was measured in the sitting position’. The office BP was measured in the supine position as stated in the *Lancet* and the letter above. Indeed, the description in the *American Journal of Nephrology* was wrong. With regard to the drug-taking protocol, however, the patients took other medications including antihypertensive agents except for RAS-blocking agents. As mentioned in the *Lancet*, using small doses the RAS-blocking agents were gradually and very carefully up-titrated to the fixed doses. The office BP would be greatly influenced by baseline therapy. The frequency of measuring office BP was twice for each patient at the start of this trial. But, soon afterward it was found by the nurses that twice was not sufficient for accurate measurement of the office BP. Therefore, we asked the independent ethical committee to increase the frequency. They did not judge it as a break in protocol and allowed us to increase the number of measurements.

I deeply apologize for our serious mistakes that you have pointed out, and thank you very much for your concern with regard to our study.

Naoyuki Nakao

To the Editor: I wish that the follow-up response from Dr. Nakao with an acknowledgement of the data management errors and the providing of the ostensibly corrected data for table 3 would have resolved the issues of concern. Unfortunately, despite these corrections and a complete re-review of the ambulatory BP data as per Dr. Nakao, there are clearly still some major problems. Apparently, the complete re-review of the data missed these residual

errors, this time primarily pertaining to diastolic BPs. Just to illustrate the most obvious ones, the 24-hour diastolic BP averages at baseline, and at the 6-month time point for each of the 3 treatment groups are lower than both the nighttime and daytime values, a physical impossibility, as has previously been pointed out for some of the systolic BP values. For the 1-year time point, the 24-hour averages for diastolic BP are equal to or 1 mm Hg higher than the nighttime diastolic pressures, while the daytime diastolic BPs are 8–9 mm Hg higher than the nighttime diastolic pressures!

With respect to the drug-taking protocol in relation to the office BP measurements, Dr. Nakao now states that the patients took all other medications including antihypertensive agents, except for the RAS-blocking agents, before the office BP measurements. However, the previous explanation letter (response) stated that the patients were requested to take all their agents *including* interventional medications (between 5 and 7 a.m.).

I am not sure what to make of these changing explanations, but I do believe that this entire correspondence and the serial corrections need to be made a part of the published record in the journal.

Anil Bidani

In Response: After inquiring into the two major issues stated by the Associate Editor, one of which is a peculiar problem, we would like to present our final response. With regard to the table, the major, still residual problem was caused partly by inappropriate data management of missing data using bugged software included in previous ambulatory BP measurement equipment and partly by incorrect insertion of data into each column. We supply a new table here (table 1). As to the latter issues, as the Associate Editor commented, the patients included in the ambulatory BP measurement substudy took all medications on each morning, not ‘the patients took all other medications including antihypertensive agents except RAS-blocking agents’.

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