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In response to 'benefits and risks of intensive blood-pressure lowering in advanced chronic kidney disease'

We thank Dr. A. Cheung and his colleagues from the SPRINT Research group for their letter-to-the-editor [1] about our study [2]. Their main criticisms included the statistical power of our study (especially in the subgroups of patients with eGFR $<45 \text{ mL min}^{-1}/1.73 \text{ m}^2$) and the issue of multiple comparisons. In our rebuttal, we take the advantage of this opportunity to clarify several core concepts of our study, highlighting the heterogeneity within the chronic kidney disease (CKD) spectrum and the statistical methods used to evaluate treatment effect modifications.

The definition of CKD is based on the single cut-off value of $60 \text{ mL min}^{-1}/1.73 \text{ m}^2$ because eGFR values $<60 \text{ mL min}^{-1}/1.73 \text{ m}^2$ are consistently associated with higher risk of adverse clinical outcomes [3]. This simple definition is useful to identify individuals at potential risk of such events associated with decreased kidney function as acute kidney injury (AKI), end-stage renal disease, cardiovascular events and death. However, the relative risk increases linearly with lower eGFR below $60 \text{ mL min}^{-1}/1.73 \text{ m}^2$ [3], and several studies have demonstrated distinct differences in patient characteristics and in absolute risk of outcomes even between patients with eGFR 30-45 vs. 45-60 $\text{mL min}^{-1}/1.73 \text{ m}^2$ [4]. Although the study population of the SPRINT appeared more homogeneous, their risk of adverse outcomes still varied substantially across eGFR categories, according to the KDIGO risk stratification table (Fig. 1; unpublished data) [3]. Indeed, 75% of 1687 SPRINT participants with eGFR 45-60 $\text{mL min}^{-1}/1.73 \text{ m}^2$ were in the 'moderately increased risk' category, whereas all 871 subjects with eGFR $<45 \text{ mL min}^{-1}/1.73 \text{ m}^2$ were in either the 'high risk' or 'very high risk' categories. Patients with eGFR $<45 \text{ mL min}^{-1}/1.73 \text{ m}^2$ also had higher levels of urinary albumin excretion and received more antihypertensive agents. Furthermore, we demonstrated that in the intensive blood-pressure (BP) control group, patients with lower eGFR achieved higher systolic BP and lower diastolic BP levels, resulting in higher pulse pressure [2]. These observations suggest a heterogeneity in the SPRINT CKD population in terms of both patient

characteristics and response to intensive BP control measures, and question the validity of the approach to categorize them into a single group.

Articles reporting the results of the SPRINT have used a strategy of dichotomization (i.e. categorizing patients into the CKD and non-CKD groups) when examining the effect modification of treatment effect by kidney function [5, 6]. However, the dichotomization of continuous variables in clinical trials has been strongly criticized [7] because it results in loss of statistical power and more potential for bias, as explained in greater detail by the Prognosis Research Strategy group [8]. Statistical power for assessing effect modification in clinical trials is generally suboptimal because such studies are designed primarily for the assessment of main effects. As dichotomization further reduces the power, it is not surprising that the prespecified treatment interaction and 'numerous subsequent post hoc analyses' from the SPRINT Research group did not reach statistical significance. Indeed, we confirmed that the *P* value for the interaction term decreased with the increase in the

		Albuminuria categories		
		A1	A2	A3
GFR categories	G1	1325	205	12
	G2	4116	618	66
	G3a	1267	366	54
	G3b	428	206	83
	G4	45	76	33

Fig. 1 The distribution of the 8900 SPRINT participants with available data on eGFR and urinary albumin, based on the KDIGO risk stratification table (unpublished data). Green, low risk (61%); yellow, moderately increased risk (23%); orange, high risk (10%); red, very high risk (6%).

number of eGFR quantiles with statistical significance for the decile groups and continuous eGFR (Table 1; unpublished data for quantiles). We would caution against using potentially false-negative results to conclude that all patients with CKD have an identical response to strict BP control as those with normal kidney function, as such over-enthusiastic generalization may overlook key predictors of the treatment effect that can potentially be used for precision medicine or individualized therapy in future clinical practice.

With that said, we would like to correct several misconceptions about our statistical approach. First, we evaluated a 'trend' of the treatment effect across the entire range of eGFR levels based on the interaction term using eGFR as a continuous variable. This model assumes 'a linear relationship (...) between the effect of the treatment and baseline eGFR' but retains greater statistical power with less bias than the model using the dichotomized variable (i.e., CKD) as explained above. Given that this interaction turned out to be significant in the direction towards increasing hazard ratio with lower eGFR, we categorized patients into four eGFR groups according to the conventional CKD staging system and focused on the lowest eGFR group. Our approach was rooted in physiologic considerations; we did not employ 'data dredging', and we only used the original primary outcome of the SPRINT for assessing the benefit of intensive BP control. Additionally, according to Rothman [9], adjustment for multiple comparisons is not warranted when

there is biologic plausibility. Therefore, the concern about multiple comparisons is not applicable to our main results. Cheung *et al.* also stated that our evaluation of the effect modification by eGFR 'depends on variations in the hazard ratio amongst the 6674 (71.6%) of the SPRINT participants analysed with baseline eGFR $60 \text{ mL min}^{-1}/1.73 \text{ m}^2$ or greater'. However, statistical power depends more on the number of events than the number of patients, and the number of events for the primary outcome was 77 (14%), 249 (44%), 127 (23%) and 108 (19%) amongst patients with eGFR >90 , $60\text{-}90$, $45\text{-}60$ and $<45 \text{ mL min}^{-1}/1.73 \text{ m}^2$, respectively. Therefore, our estimation of the effect modification by eGFR was driven by a wide range of eGFR levels, which was also supported by Figure 3 in our original article showing a good potential of linearity in the hazard ratios including the one in the category of eGFR $<45 \text{ mL min}^{-1}/1.73 \text{ m}^2$ [2].

Cheung *et al.* contend that the hazard ratio of 0.92 (95% confidence interval, 0.62 to 1.38) for the primary outcome within the subgroup with eGFR $<45 \text{ mL min}^{-1}/1.73 \text{ m}^2$ is consistent with a potential substantial benefit as reported in their publication [5, 6] based on the range of the 95% confidence interval extending to 0.62. However, this interpretation ignores the significant effect modification towards inflating hazard ratio with lower eGFR. Furthermore, the actual numbers of events/participants ratio amongst patients with eGFR $<45 \text{ mL min}^{-1}/1.73 \text{ m}^2$ were 54/446 and 54/445 in the intensive and standard BP control groups, respectively [2]. Although the SPRINT was not intended to provide adequate power for any subgroup analyses, this small difference in the actual numbers of events/participants ratio makes a substantial benefit from the intensive BP control unlikely in this population.

Cheung *et al.* also point out the potential for ascertainment bias for AKI because 'there were 30% more unscheduled visits in the intensive SBP group than in the standard SBP group'. However, we used a variable for AKI that was considered as a serious adverse event by SPRINT, namely that was 'coded if the diagnosis was listed in the hospital discharge summary and was believed by the safety officer to be one of the top three reasons for admission or continued hospitalization' [5]. The SPRINT data set contained another variable for AKI which included those coded at the emergency department, but it was not used in our study. Therefore, unscheduled visits should not have

Table 1 P_{trend} values for the interaction terms with intensive blood-pressure control across different definitions for eGFR categories (unpublished data for quantiles)

eGFR subgroups	P_{trend} for interaction
CKD (SPRINT) [5]	0.364
Quantiles	
2 (median)	0.169
3 (tertile)	0.130
4 (quartile)	0.160
5 (quintile)	0.053
6 (sextile)	0.082
7 (septile)	0.062
8 (octile)	0.086
10 (decile)	0.047
Continuous (Our study) [2]	0.019

affected our findings. As Cheung *et al.* mentioned, there is also some possibility that unmasked healthcare providers coded 'AKI' in the hospital discharge summaries of patients in the intensive BP group more frequently, even if they did not experience significant changes in serum creatinine. However, this ascertainment bias may also go towards the opposite direction favouring the intervention. The SPRINT protocol minimized such risk of bias by employing the judgement of an adjudication panel who were masked to the treatment assignments. As we used the outcome of AKI as defined by the SPRINT Research group and as reported by both main and multiple ancillary studies of the SPRINT [5, 6], we are surprised that Cheung *et al.* questions the validity of our approach. The important issue here is how much and in what direction this possible bias had actually influenced the ascertainment of AKI, which needs to be quantified for further discussion.

Lastly, Cheung *et al.* mentioned that the majority of AKI events were judged as stage 1 and that most elevated serum creatinine levels returned to within 20% of pre-existing values. However, previous studies have demonstrated that even stage 1 AKI is associated with mortality amongst hospitalized patients [10] and that amongst patients with CKD, those who suffered from AKI experience a higher incidence of end-stage renal disease after hospital discharge even if they recover their kidney function [11]. Further investigations are needed to examine how much the intensive BP control-induced AKI impacts long-term hard clinical outcomes so that we can consider the risk-benefit balance of intensive BP control more precisely, but as a matter of general principle AKI should not be engendered in a population where the intervention causing it is less likely to confer benefit.

One of the purposes of data sharing, as done with the SPRINT data set by the National Heart, Lung, and Blood Institute (NHLBI) BioLINCC repository, is to facilitate further research that can help advance scientific discovery and improve clinical care by stimulating independent ideas. Although all post hoc analyses are hypothesis-generating, we believe that our study has added relevant information to the current knowledge in managing hypertension amongst patients with CKD. Our findings, *vis-à-vis* those published from the SPRINT Research group, should be presented in a balanced format to clinicians, patients and the scientific

community from one versus the other before drawing far-reaching conclusions about the ideal blood-pressure target in the CKD population.

Conflict of interest statement

Dr. Obi reports honoraria and/or support from Ono and Chugai, outside the submitted work. Dr. Kalantar-Zadeh has received honoraria and/or support from Abbott, Abbvie, Alexion, Amgen, the American Society of Nephrology, Astra-Zeneca, Aveo, Chugai, DaVita, Fresenius, Genentech, Haymarket Media, Hospira, Kabi, Keryx, the National Institutes of Health, the National Kidney Foundation, Relypsa, Resverlogix, Sanofi, Shire, Vifor and ZS-Pharma, outside the submitted work. Dr. Kovesdy reports grants from NIH/NIDDK during the conduct of the study; personal fees from Amgen, Sanofi-aventis, Fresenius Medical Care, Keryx, Bayer, Abbott and Abbvie; and a grant from Shire, outside the submitted work. Dr. Hamano has received honoraria and/or support from Chugai, Otsuka, Torii, Kissei, Kyowa Hakko Kirin, Terumo, Fuso, Eisai and Takeda, outside the submitted work.

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