Response to the Letter to the Editor Entitled "A Critical Appraisal of End Points and Statistical Strategies in the DIDo Trial"

The Author Replies: We thank Himanshu *et al*.[1] for their comments regarding our DIDo study.[2] Their critique indeed highlights several important methodological and interpretative aspects that deserve consideration.

We fully acknowledge and agree with the following key points they raised: (i) the limitations of the study inherent to the use of composite end points, which may obscure the effects on pathophysiologically distinct outcomes; (ii) the reduced statistical power because of the lower-than-planned sample size; (iii) the importance of integrating patient-centered outcomes to enhance clinical relevance; (iv) the potential applicability of genetic determinants, such as AQP-1 polymorphisms, for tailoring peritoneal dialysis strategies[3]; and (v) the absence of icodextrin metabolites determination. All these points had been mentioned as limitations in the discussion of our study.

With respect to the first 2 aspects, we concur that the composite primary end point may have diluted the specific effect of the double icodextrin dose on ultrafiltration. However, given the exploratory nature of this randomized trial, we considered that capturing several clinically meaningful events was necessary to provide a pragmatic picture of the intervention's impact, especially in a population of older patients, as was the case in the DIDo study. Similarly, we recognize that the sample size did not reach the planned target for multiples reasons. Nevertheless, the observed trends remain consistent with the hypothesized effects, suggesting that the reduced sample size is unlikely to have substantially altered the overall interpretation of the results.

Regarding the other points, we emphasize that data on both AQP-1 genotypes and health-related quality of life (SF-36 questionnaires) were collected during the trial in a large proportion of the patients. These analyses are ongoing, and we expect them to provide valuable complementary insights, particularly for identifying potential responder subgroups and better capturing the patient's lived experience. In addition, we are actively looking for a laboratory where the measurement of the icodextrin metabolites could be performed to clarify their potential impact on low sodium concentration.

In summary, though we acknowledge the limitations highlighted, we believe that they do not alter the main message of the DIDo study; a conclusion that was also mentioned by the accompanying editorial.[4] On the contrary, integration of the forthcoming analyses on AQP-1 genotypes, quality of life, and icodextrin metabolites will further strengthen the translational value of our study and contribute to advancing a more individualized and patient-centered approach for peritoneal dialysis in older patients.

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