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# Interdialytic Weight Gain and Hemoglobin Concentrations in the Japanese Dialysis Outcomes and Practice Patterns Study: Further Considerations



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The clinical excellence of Japanese hemodialysis practice can hardly be overestimated, as substantially better outcomes have consistently been reported for Japan in comparison with other nations. In a narrative review,<sup>1</sup> written on receiving the David M. Hume Memorial Award, Friedrich K. Port recapitulated that better survival among Japanese versus US hemodialysis patients became evident as early as 1990, through comparison of registry data.<sup>2</sup> By initiating the international Dialysis Outcomes and Practice Patterns Study (DOPPS), Dr. Port and colleagues responded to the critical need of studying ways to improve care and outcomes for hemodialysis patients in the United States. In consequence, Japan was among the first countries whose hemodialysis data were recorded and analyzed in DOPPS.

The current issue of *Kidney International Reports* now includes

an analysis from the Japanese (J) DOPPS alone. Using J-DOPPS data, Takashi *et al.*<sup>3</sup> found that hemodialysis patients in the highest interdialytic weight gain (IDWG) category of  $\geq 6\%$  had a higher risk for major adverse cardiovascular events if their hemoglobin (Hb) concentration was  $\geq 11.0$  to  $< 12.0$  g/dl, when compared with patients with an Hb concentration  $\geq 10.0$  to  $< 11.0$  g/dl. The relative excess risk due to interaction between IDWG and Hb was 0.22, and the corresponding 95% confidence interval excluded zero, indicating a synergistic interaction between Hb and IDWG on major adverse cardiovascular events.<sup>3</sup> This study brings to light several questions worth discussing regarding its definitions, outcomes and analysis.

## How Can IDWG Best Be Defined, When Should IDWG Be Assessed in an Analysis of Outcomes, and How Large Does the Population at Risk Have to Be, in an Association Study?

In the article by Takashi *et al.*,<sup>3</sup> IDWG was expressed as a percentage

(without specifying whether this percentage referred to pre- or postdialysis *body weight*). Intradialytic weight loss was used as a proxy for IDWG and was assessed in the first session of the week at the enrollment into J-DOPPS. This approach, however, is not optimal and is not consistent with the most recent international DOPPS analysis, which used actual weight data (predialysis body weight minus postdialysis body weight of the previous hemodialysis session) from 3 consecutive dialysis sessions rather than from the first session of the week, calculating IDWG in percentage of postdialysis weight.<sup>4</sup> The approach used by Takashi *et al.*<sup>3</sup> permitted including patients from the earliest DOPPS phase (1996–2001), where only intradialytic weight loss was available, and this strategy might have increased the fraction of patients with relatively high weight gains (IDWGs), who were more prevalent in the earlier DOPPS phases.<sup>4</sup> However, using the first hemodialysis session of the week after the long interdialytic interval inevitably increases the number of patients with high IDWGs. Of note, the number of patients who actually fulfilled both criteria, high Hb and high IDWG, was small in this study: 230 of the entire study data set of 8234 patients (= 2.8%, deduced from Table 2 from Takashi *et al.*<sup>3</sup>).

## Which Statistical Approaches Can Be Used to Analyze the Association Between IDWG and Mortality?

In the article by Takashi *et al.*,<sup>3</sup> the association between IDWG and mortality was assessed with a Cox model that used only IDWG at baseline (which encompasses the shortcoming of the single IDWG assessment specified previously). The most recent international DOPPS analysis also used a Cox model, where time at risk started at the baseline IDWG data collection.<sup>4</sup> Both analyses excluded

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patients with hemodialysis vintage <6 months<sup>3</sup> and <12 months,<sup>4</sup> respectively. In contrast to these approaches,<sup>4</sup> the perhaps most prominent analysis of IDWG and mortality, published by Kamyar Kalantar-Zadeh *et al.*<sup>5</sup> in 2009, used time-dependent (quarterly varying) Cox models that included IDWG as a repeated measure, averaged over each 13-week calendar quarter. Calculating the 13-week averaged predialysis and postdialysis weights for each patient during each of the calendar quarters of the cohort meant that up to 39 dialysis treatments per calendar quarter were considered.<sup>5</sup> The association between IDWG and mortality, however, differs according to the statistical model (time-dependent vs. baseline model) that is used.<sup>6</sup>

### What Is the Risk Associated With Low IDWG Among the Highest-Risk Patients, Namely Those Who Have Low, Not High, Hb Concentrations?

Patients who have high IDWGs should not automatically be equalized with patients who have chronic volume overload.<sup>7</sup> Of note, when Hecking *et al.*<sup>6</sup> recently analyzed data from NephroCare, the highest mortality risk association was observed in the group of patients with low IDWG and chronic fluid overload, as shown by bioimpedance spectroscopy. In contrast to previous analyses, we statistically considered IDWG (i) as a time-varying 1-month average, (ii) as a time-varying 12-month moving average, and (iii) as a long-term risk factor, which we believe was an adequate compromise between the approaches taken by Kalantar-Zadeh *et al.*<sup>5</sup> versus by the DOPPS group.<sup>4</sup> With regard to the present study, the highest risk association (mortality and major adverse cardiovascular events) was observed in patients who had low

Hb concentrations and low IDWGs (Tables 4 and 5 from Takashi *et al.*<sup>3</sup>), but was downplayed as being due to inflammatory factors that “could not be adjusted for.” According to Table 2 from Takashi *et al.*<sup>3</sup>, the number of patients at risk was substantially higher than those 2.8% with an Hb concentration  $\geq 10.0$  to  $< 11.0$  g/dl and IDWG  $\geq 6\%$ , and this number would likely have been much higher still, if patients with vintage <6 months had not been excluded. Patients with low Hb and low IDWG, on top of being inflamed, could be suffering from chronic fluid overload, and their low Hb concentrations could indicate hemodilution combined with malnutrition, as indicated by the lower albumin levels in these patients. Asking patients the simple question: “Have you *recently* stopped eating?” during rounds could help identify those patients who are likely at the very highest risk.

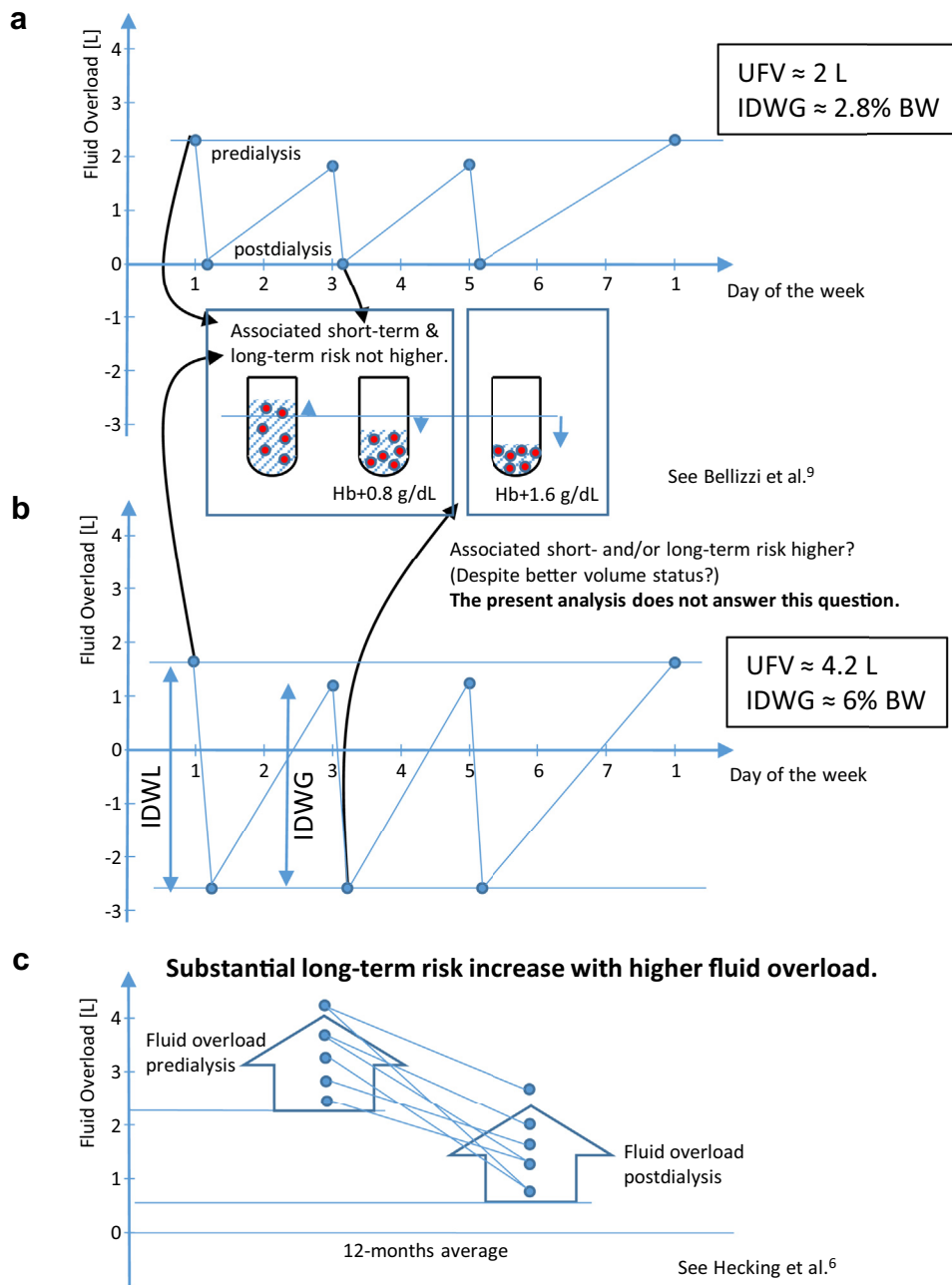
### Could Patients With High IDWGs Be Dehydrated Postdialysis, Especially in Japan Where Patients Have the Highest IDWGs Among All DOPPS Countries?

The first international DOPPS publication on nonadherence<sup>8</sup> found that IDWG  $> 5.7\%$  of dry weight was most prevalent in Japan, although (as was also indicated by other nonadherence measures) Japanese patients are likely among the most “adherent” individuals worldwide. The most recent international DOPPS publication on IDWG confirmed that IDWGs are higher in Japan than in the other DOPPS countries.<sup>4</sup> One reason for this finding might be higher salt consumption, and an indicator for this hypothesis could be the fact that hemodialysis patients in Japan have higher serum sodium

concentrations than patients in most other DOPPS countries.<sup>4</sup> Another plausible reason could be an excellent (somewhat dehydrated) volume status postdialysis in Japanese patients. Although data from Japan and the United States are not recorded in NephroCare, the analysis of this data set has shown that IDWG can be positively predicted by bioimpedance spectroscopy-proven fluid overload predialysis, and negatively predicted by fluid overload postdialysis.<sup>6</sup> Conceptually, this finding means that thirst induced by postdialysis dehydration cannot be ignored by patients, and some of the highest IDWG patients might be relatively more dehydrated. Lower levels of fluid overload in Japan could thus be one of the reasons for substantially better outcomes in this country. However, the latter theory is currently speculative.

### Has the Relationship Between Hb and IDWG Been Disentangled, and if Not, What Should Be the Next Analytical Steps?

When Takeshi *et al.*<sup>3</sup> stated that the interaction between Hb and IDWG is not well understood, they cited a study that thoroughly evaluated Hb concentrations in a small cohort: before and after hemodialysis, after the long and the short interdialytic interval.<sup>9</sup> This study suggested that the *short* interdialytic period is the most appropriate timing for anemia assessment, but otherwise focussed on the short-term changes in Hb in consequence of the ultrafiltration during hemodialysis. In the data set analyzed by Takeshi *et al.*,<sup>3</sup> Hb concentrations tended to be lower in the group of patients with IDWG  $\geq 6\%$  (Table 1 in Takeshi *et al.*<sup>3</sup>), which might indicate a relationship between higher IDWG and lower Hb. Unfortunately, the



**Figure 1.** The interplay between fluid volume and hemoglobin (Hb) concentrations and risk of mortality and major cardiovascular events in hemodialysis patients. This figure illustrates the possible difference between potential short-term versus long-term risk of mortality and major cardiovascular events (including stroke/transient ischemic attack), associated with hemoconcentration through relatively high ultrafiltration volumes (UFVs) in hemodialysis patients with relatively high interdialytic weight gains (IDWGs). (a) Example of a patient with relatively normal IDWG. The patient is shown as being normohydrated at the end of the dialysis session (fluid overload = 0 liter). Only limited hemodilution in the predialysis condition and limited hemoconcentration in the postdialysis condition will occur. No additional short- and/or long-term risk will likely be associated with the interaction between IDWG and Hb. See Bellizzi et al.<sup>9</sup> (b) Example of a patient with relatively high IDWG and dehydration at the end of the hemodialysis session. Hemoconcentration is likely to occur and might lead to an increased short-term risk of mortality and major cardiovascular events (including stroke/transient ischemic attack). If the patient tolerates postdialysis dehydration, the long-term outcomes might be better, even if the short-term risk could be increased. (c) Long-term risk for all-cause mortality, independent of IDWG (or Hb concentration) may be caused by pre- and or postdialysis fluid volume overload alone. See Hecking et al.<sup>6</sup> BW, body weight.

authors did not dissect the relationship between IDWG and Hb any further, and did not report the correlation coefficient between IDWG and Hb. Thus, the

relationship between Hb and IDWG has not been disentangled, and the next analytical steps would require additional assessment of fluid overload with an

objective method. We have summarized our understanding of the interplay among IDWG, intradialytic weight loss, fluid overload, and Hb in Figure 1.<sup>6,9</sup> We

recommend future studies with additional data collection on volume status with the aim to answer the questions that have been posed by Takashi *et al.*<sup>3</sup>

## DISCLOSURE

All the authors declared no competing interests.

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