A significant fall in BP during dialysis, so-called intradialytic hypotension (IDH), is an important clinical problem. IDH is common, occurring in 15%–20% of treatments. IDH is often associated with distressing symptoms such as lightheadedness, weakness, muscle cramps, and nausea and vomiting. As could be imagined, reducing blood flow to vital organs, even transiently, is associated with a panoply of organ damage, including myocardial stunning, ischemic damage to the white matter of the brain, and perhaps disruption of the gastrointestinal barrier against endotoxins with increased inflammation. Severe IDH has been associated with a variety of catastrophes. It is likely linked to intradialytic arrhythmias, and may precipitate these, as well as myocardial infarction. Case reports of intestinal infarction, as well as of IDH-induced blindness due to retinal ischemia, have been reported. Arteriovenous access thrombosis is seen more commonly in patients with IDH. Finally, in patients with residual kidney function, repeated ischemic insults to a kidney unable to autoregulate its blood flow may hasten the progression to anuria and loss of the substantial advantages that even small amounts of residual kidney function provide. Some of the cardiovascular event risk associated with IDH may be a reflection of underlying comorbidity. The risk of IDH increases markedly at low values of predialysis BP, and low predialysis BP has itself been associated with cardiovascular disease and increased short-term mortality risk. However, it is very likely that repeated ischemic insults to various body organs caused by IDH are causally linked to poor outcomes including mortality.

The root cause of IDH is fluid removal. If one dialyzes a patient and does not remove fluid, the occurrence of IDH is rare to nonexistent. Two aspects of fluid removal are important: the rate of removal, and the amount of fluid removal. During the early part of a dialysis session, when most excess fluid is located closer to the central circulation, higher rates of fluid removal are tolerated. By contrast, toward the end of a dialysis session, the same rate of fluid removal might result in hypotension, because the slow rate of fluid transfer from distal edematous body compartments to the circulation results in poor vascular refilling, reduced cardiac output, and thus IDH.

One can think of fluid removal on a weekly time scale. Fluid removal depends on the weekly amount of fluid ingestion, and this in turn is driven primarily by sodium intake. Diffusive gain of sodium from the dialysis solution is also a factor when higher dialysis solution sodium concentrations are used. Weekly fluid removal also depends on the daily urine volume, which represents ingested fluid that does not need to be removed by dialysis. After residual kidney function has been taken into account, the remaining ingested fluid needs to be removed by dialysis, and the sole determinant of the required ultrafiltration rate will be weekly dialysis time. Dividing up a fixed amount of dialysis time into intervals more frequent than three per week is an attractive option theoretically, because then more fluid should be closer to the central circulation at the time of attempted removal. However, in patients in the Frequent Hemodialysis Network Daily Study who were assigned to therapy six times per week, the weekly frequency of IDH was slightly increased relative to the group assigned to conventional thrice-weekly treatments. This was due to the greater number of dialysis treatments given in the frequently dialyzed group, as the rate of IDH per treatment was reduced. Moving to a more frequent dialysis schedule is associated with a reduction in predialysis BP and a reduced need for antihypertensive medication. Avoidance of the long weekend intradialytic interval is another benefit of adding more treatments per week. With regard to fluid removal needs, one might achieve a considerable reduction in IDH by encouraging patients to eat less sodium, by avoiding high dialysis sodium concentrations, and by increasing weekly dialysis time.

An equally important issue with regard to IDH may be the volume of the extracellular fluid (ECF) postdialysis. Using a multifrequency bioimpedance device, one can more rationally target an “optimum” postdialysis weight, based on a comparison of bioimpedance-estimated ECF compared with ECF of healthy patients of similar age, sex, and body size. It is not yet known to what extent the ideal ECF suggested by these devices indicates the true “optimum” level in a given dialysis patient, particularly as modulated by cachexia/obesity and general health. In addition, it is not known whether one should decrease the ECF to this optimum level at the end of dialysis or if one should dip slightly below it in order to
minimize ECF overload during the interdialytic period. Aggressive attempts to control BP and/or fluid overload without bioimpedance guidance have been associated with an increased frequency of IDH, and possibly increased risk of arteriovenous access failure and even cardiovascular hospitalization. By contrast, increasing the postdialysis ECF level based on bioimpedance guidance in a subset of patients has been reported to reduce interdialytic weight gain, and even to result in resumption of residual kidney function (J.E. Tattersal, personal communication).

In terms of IDH, a key role is played by thermal energy balance. Almost all studies that have looked at the effect of lower dialysis solution temperature on frequency of IDH have found marked reductions. Cool-dialysate use has been associated with reduced postdialysis recovery time, reduced myocardial stunning, and reduced structural damage to brain white matter. Some, if not all, of the increased tolerability of hemodiafiltration may be due to thermal effects. Use of lower-temperature dialysate has been associated with reduced cardiovascular mortality, and it is possible that some of the "hard outcomes" benefits of high-volume hemodiafiltration in terms of fewer cardiovascular events may be due to slight cooling associated with this therapy. Use of pharmacologic aids to maintain BP during dialysis, such as midodrine or sertraline, have no additive benefit if given to patients being dialyzed with cool-temperature dialysate.

Some advanced dialysis machines provide tools that may limit the occurrence of IDH. Many dialysis machines are equipped with the ability to vary dialysate sodium during a treatment, with or without concomitant variation of the ultrafiltration rate. Perhaps this approach is most useful when combined with continuous estimates of plasma volume by following the degree of hemoconcentration in the course of a dialysis session as fluid is removed. No method has been devised to measure central translocation of red blood cells from the splanchnic venous pool during fluid removal. This hypovolemia-associated central shift of red blood cells might be impaired in patients with autonomic dysfunction, and might be augmented by drugs that preferentially constrict the splanchnic vascular bed such as vasopressin.

With so many different approaches available to reduce the incidence of IDH, and the ability of dialysis machines to automatically communicate details of individual dialysis treatments to centralized databases, large dialysis organizations have a unique opportunity to track the occurrence of IDH and to determine to what extent the application of various quality improvement measures reduces its incidence. To accomplish this, one needs to have a definition of IDH that is unambiguous and, ideally, is associated with meaningful outcomes. In this issue of JASN, using archived data from the Hemodialysis (HEMO) study, Flythe et al. examined IDH as defined by each of eight different criteria, and explored to what extent each definition of IDH associated with all-cause 1-year mortality. The first definition of IDH in the HEMO data had been prospectively defined, and required either a slowing of the ultrafiltration rate or infusion of saline associated with symptoms. According to this interventional definition, IDH increased the risk of 1-year mortality (relative risk, 1.46; 95% confidence interval, 1.13 to 1.88), but the risk was attenuated to 1.01 after multivariable logistic regression adjustment. The authors also looked at a number of other definitions of IDH, including lowest (nadir) systolic BP during a treatment (<90 or <100 mmHg). Other definitions included a combination of nadir systolic BP<90 or <100 mmHg plus either symptoms or intervention, or a fall in systolic BP by at least 20 or 30 mmHg, or the combination of a fall in systolic BP of 20 or 30 mmHg plus a nadir BP of <90 mmHg. Many of these alternative prespecified definitions were used in previously published studies of IDH or were suggested by various guideline groups. Flythe et al. found that IDH defined as nadir systolic BP<90 mmHg was the best predictor of mortality in both the HEMO and large dialysis organization patient data sets, whereas a nadir <100 mmHg was the best predictor of mortality in the subgroup with predialysis systolic BP>160 mmHg. Their findings could be interpreted to suggest that even asymptomatic IDH is associated with markedly increased mortality risk, because definitions of IDH requiring symptoms or intervention did not increase the association with mortality risk. The authors commendably went through a number of steps to minimize the risk of confounding of mortality risk associated with IDH and mortality risk associated with low predialysis BP. They did this by a matching analysis, in which participants with IDH were matched against similar participants without IDH at similar levels of predialysis systolic BP. The increased mortality risk due to IDH persisted in the BP-matched cohorts.

The findings by Flythe et al. are important and should be a great help to large dialysis organizations and other dialysis care providers in tracking IDH occurrence in their patients, and in evaluating the success of various quality improvement measures aiming to reduce the incidence of IDH. Whether a definition based on a nadir systolic BP<90 mmHg can rise to the level of a full-fledged surrogate outcome is not clear, but this is an easy measurement to extract from a dialysis session and track, and the association of IDH defined in this way with mortality justifies choosing it as a useful quality improvement measure.

This analysis by Flythe et al., along with other analyses of archived HEMO study data by Flythe et al. and others, testifies to the utility of those National Institutes of Health–funded randomized trials in which the trial data have been made available to a wider group of investigators after conclusion of the primary and main secondary analyses; these scientists are now creatively looking at the data to answer clinical questions that had not been foreseen in the original study designs.

DISCLOSURES
None.

REFERENCES
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