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Effect of Membrane Permeability on Survival of Hemodialysis Patients

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The biologic plausibility of clinical benefits of high-flux compared with low-flux hemodialysis is supported by observations that numerous molecules with known biologic activities and potentially harmful effects accumulate in the plasma of patients with ESRD and are preferentially cleared by high-flux dialysis. In addition to β_2-microglobulin, which is often used as a plasma marker, examples of these toxic middle molecules include parathyroid hormones, advanced glycation products of various molecular weights,[1] leptin,[2] apolipoprotein C-III,[3] and several molecules that inhibit granulocyte functions.[4] Empirical support for the clinical benefits of high-flux dialysis is provided by observational studies that report associations of high-flux dialysis with reduced mortality[5]; however, the Hemodialysis (HEMO) Study, a randomized trial performed in 1846 hemodialysis patients in the United States between 1995 and 2001, failed to demonstrate a decrease in its primary end point of all-cause mortality (hazard ratio [HR] 0.92; 95% confidence interval [CI] 0.81 to 1.05) with high-flux compared with low-flux dialysis.[6] Nonetheless, because the lower limit of the CI could not rule out an overall hazard reduction of up to 19% and because secondary analyses showed trends favoring high flux for all-cause mortality in patients with >3.7 yr of previous dialysis[7] and for cardiac mortality in the full cohort,[6,8] the possibility of a moderate benefit of high-flux dialysis could not be excluded definitively.

The seminal report of the randomized comparison of high-flux *versus* low-flux groups in the Membrane Permeability Outcome (MPO) Study by Locatelli *et al.*[9] in this issue of *JASN* provides valuable new information on this important question. Because the precision of estimated HRs depends on the number of outcome events, the precision of the MPO Study, with 162 deaths, was less than that of the HEMO Study, with 871 deaths[6]; however, the MPO Study provides key information on the effect of flux in a different setting. For example, MPO Study patients were more likely than the HEMO Study patients to be white and to use native fistulas[10] and tended to

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have lower comorbidity than the HEMO Study patients (24 *versus* 45% with diabetes and 27 with cardiovascular disease *versus* 80% with cardiac disease at baseline, and 8.2 *versus* 16.6 deaths per 100 patient-years during the trial[6]). Perhaps more important, the MPO Study enrolled incident hemodialysis patients, whereas the mean dialysis duration at entry in the HEMO Study was 3.7 yr. By studying incident patients, the MPO Study avoided the complication that the treatment effects might be altered by previous exposure to low-flux or high-flux dialysis but incurred the risk that enhanced dialytic middle-molecule removal by the high-flux intervention might be overshadowed by residual kidney function in the months or years close to dialysis initiation.

There were also key differences between the trial interventions and conduct. In contrast to the HEMO Study, which was performed in a setting of predominant dialyzer reuse,[11] dialyzers in the MPO Study were not reused. Requirements for inclusion of low-flux and high-flux dialyzers were based on membrane β_2-microglobulin sieving coefficients in the MPO Study. In contrast, mean clinical β_2-microglobulin clearances were used as part of the criteria in the HEMO Study.[6,7,11] The use of different definitions for high flux complicates the comparison of membrane permeability, although it is possible that the high-flux arm in the MPO study had a higher mean β_2-microglobulin clearance than the high-flux arm in the HEMO Study.

The primary analysis of the effect of high flux on mortality in the full MPO Study cohort indicates a trend favoring high flux that did not reach statistical significance; however, the MPO Study reports a statistically significant interaction of the flux intervention with baseline serum albumin level, with a nominally significant benefit reported in the subgroup characterized by serum albumin $\leq$4 g/dl (HR 0.63; 95% CI 0.45 to 0.90). Thus, the interpretation of the MPO Study is centrally related to the general problem of interpreting positive subgroup results in the setting of a negative finding in the full cohort. The evidence supporting a benefit in patients with hypoalbuminemia is strengthened because this subgroup was the original targeted population of the trial,[9,12] and separate analyses for the two albumin subgroups were preplanned when the subgroup with normoalbuminemia was added. This *a priori* focus on the subgroup with hypoalbuminemia reduces the likelihood of a spurious finding as a result of multiple comparisons. This stands in contrast, for example, to the HEMO Study subgroup result in patients with $>$3.7 yr of previous dialysis, which was investigated as one of seven subgroup factors, although the subgroup analyses were also preplanned. Nonetheless, the plausibility of the positive MPO finding in the subgroup with hypoalbuminemia is somewhat reduced by the absence of a similar finding in the HEMO Study, which found no evidence of a greater benefit of high flux in patients with hypoalbuminemia.[7]

Joint analyses of the HEMO and MPO databases may be useful for further investigation of the combined evidence from these two studies. At this point, our best assessment of the range of the plausible benefits of high flux is provided by the 95% CIs for the mortality HRs in the full cohorts corresponding to the settings of the two studies, which were 0.81 to 1.05 and 0.56 to 1.04 in the HEMO Study and MPO Study, respectively. Given relatively strong arguments for the biologic plausibility of advantages of high flux, these intervals can be considered to be consistent with some clinical benefits of high flux, although they leave open the possibility of no benefit because both intervals overlap with 1.0. Of importance, neither the MPO Study nor the HEMO Study suggested harmful effects associated with high flux. It is yet to be determined whether more definitively positive results can be observed using membranes or techniques that permit even greater removal of middle molecules, such as hemodiafiltration, which achieves β_2-microglobulin clearances of $>$100 ml/min.[13] In the meantime, despite some remaining uncertainty, the results of the MPO Study can be interpreted as a supporting rationale for the use of high-flux dialysis membranes if they are financially affordable.

DISCLOSURES

A.K.C. and T.G. were investigators in the HEMO Study. A.K.C. is also a consultant of Baxter Corporation.

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