

Charting New Territory by Simulated Modeling of a Clinical Trial

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Cardiovascular disease (CVD) remains one of the most common comorbidities and causes of death among patients who are treated for ESRD by hemodialysis (1). On the basis of an extensive body of clinical trial evidence, across a spectrum of high CVD risk states from prevalent disease to primary prevention, statin therapy for LDL cholesterol lowering has emerged as one of the most important strategies to reduce risk in populations without ESRD (2–5). By logical extension, two clinical trials to date (Die Deutsche Diabetes Dialyze Studie [4D Study] and A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events [AURORA]) evaluated whether statin therapy was effective for CVD risk reduction in patients with hemodialysis-treated ESRD (6,7). Neither study found a statistically significant benefit on the primary outcomes, whereas some indication of harm related to statin therapy emerged.

The intent of the article published in this issue of *CJASN* by Chan *et al.* (8) was to substantiate—or not—outcomes of statin therapy among hemodialysis patients who have diabetes and are being treated in everyday medical practice by means of a simulated clinical trial model. Their innovative approach was enabled by a large clinical sample, electronic medical records, and advanced software programs that provided more complete control for covariates and residual confounding (especially as related to statin indication and dosage) compared with more traditional statistical analyses. The authors were clear to point out that these types of studies, which are observational and retrospective in nature, do not replace clinical trials. Rather, such approaches provide opportunity to strengthen or generate hypotheses for prospective testing and to validate clinical trial results in a “real world” environment.

By using the same eligibility criteria as in the 4D Study, the simulated model “enrolled” a highly similar yet substantially larger population compared with the original study (8). New users of statins were selected from the electronic medical records of a national sample of patients who had type 2 diabe-

tes and were undergoing long-term hemodialysis in Fresenius Medical Care facilities in the United States. Nonusers were selected by matching on cholesterol level and dialysis vintage to form the study cohort for subsequent propensity testing and multiple variable modeling. Statin users and nonusers were required to have been undergoing dialysis for at least 90 days without receiving a statin prescription. The resultant cohort for the simulated model included 10,288 patients, a nearly 10-fold larger sample size than in the original 4D Study.

The simulated model produced hazard ratios that were numerically similar to those observed in the 4D Study (8). Statin therapy was indeed associated with risk reductions—10% for the primary outcome (composite of cardiac death, nonfatal myocardial infarction, and fatal and nonfatal stroke), 17% for death from cardiac causes, and 18% for death from all causes—however, statistical significance for these hazard ratios was achieved with the larger sample provided by the simulated model. The original 4D Study also reported an unexpected finding that the relative risk for fatal stroke was increased approximately two-fold in the group assigned to receive atorvastatin (6). Although the explanation for this finding has been elusive, the simulated model reproduced a signal regarding statin usage and increased stroke risk in patients who have diabetes and are undergoing hemodialysis. In the latter, risk for nonfatal (but not for fatal) ischemic stroke increased by 25% in statin users, a statistically significant effect. Overall, the simulated model corroborated and extended the inferences from the original 4D Study by showing a modest benefit of statin use on death and major CVD events; however, the modeled trial also reinforced concern about potential for harm in the form of increased stroke risk in diabetic patients who are undergoing hemodialysis and take statins.

The other major study of statin therapy in hemodialysis patients published thus far has been AURORA (7). Hemodialysis patients both with and without diabetes between 50 and 80 years of age were recruited for this trial of rosuvastatin *versus* placebo. The sample size at 2776 participants was intermediate between the 4D Study and that of the simulated model trial, yet the trend toward modest benefit of statin therapy on death and major CVD events was not observed in AURORA. Moreover, these primary results held true in the predefined diabetes subgroup as well. Although stroke risk was not increased by rosuvastatin in the study population as a whole, there was a

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marginal increase in the number of strokes among the participants who had diabetes and received statin therapy.

The Study of Heart and Renal Protection (SHARP) is an international collaborative clinical trial that is nearly complete and expected to report its primary results in late 2010 (9). Results of SHARP will be crucial to defining more clearly the risks and benefits of statin therapy (combined with ezetimibe) in people with kidney disease. With a sample size of approximately 9000 participants and at least 4 years of follow-up, it will be the largest clinical trial of any sort conducted in this population so far. Importantly, the study includes a broad range of patients both with and without diabetes and with chronic kidney disease (CKD; “predialysis” approximately 6000 patients; hemodialysis or peritoneal dialysis approximately 3000 patients). As a result, it should address a number of key issues, including whether CVD benefits of statin therapy are lost with advancing stages of CKD.

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) has provided recommendations for treatment of dyslipidemia in CKD by developing clinical practice guidelines (10). After the publication of the 4D Study results, the Diabetes and Chronic Kidney Disease guidelines modified the previous KDOQI recommendations regarding dyslipidemia by stating that statin therapy should not be initiated in patients who have diabetes and are on hemodialysis unless there is a specific cardiovascular indication for treatment (11). This more conservative approach has been further substantiated by the results of AURORA (7). Even though the simulated model of the 4D Study reported significantly reduced risk for several CVD end points, these putative benefits seem modest at best (8). Importantly, the persistent signal from both clinical trials and the simulated model about increased stroke risk warrants caution about initiating statin therapy in hemodialysis patients with diabetes. In the meantime, completion of SHARP is intently awaited. Data regarding both efficacy and safety from this study should provide a rigorous evidence base on which recommendations for statin use can be further updated for a wide range of patients with CKD.

Finally, the use of electronic medical records to generate large repositories of data from disparate sources for clinical research holds great appeal, as demonstrated by the simulated model of the 4D Study (8); however, along with the promise comes potential for pitfalls, especially with regard to jeopardizing privacy and security of patient information. Use of electronic medical records will continue to grow and chart exciting new territory for research. Nevertheless, a number of important issues arise regarding appropriate use of such data, as thoughtfully articulated in recent reviews (12,13). In the case of the simulated model of the 4D Study, the requirement for institutional review board review and, by extension, informed consent was interpreted as “exempt” on the basis of the investigators’ interpretation of current US federal law; however, not all experts in health policy or clinical research would necessarily concur (12,13). Here are some fundamental questions to consider as use of electronic medical records for research moves forward (naming just a few of many):

- How can objective oversight be provided to support worthy research initiatives yet still protect unknowing patients from those who may retrieve their personal information with blind ambition or disreputable intent?
- Should requirements for institutional review board review or informed consent be uniformly waived for use of “de-identified” clinical data or specimens that exist in repositories? Is it possible truly to de-identify data, especially in settings of long-term follow-up for clinical outcomes?
- Should patients who use clinical services be informed about potential research uses of their protected health information? Can they opt out? If so, then how?

The simulated model of the 4D Study certainly has made a distinctive contribution to innovation in clinical research but also brings to light important ethical and regulatory considerations about how to conduct the process itself.

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See related article, “Modeling the 4D Study: Statins and Cardiovascular Outcomes in Long-Term Hemodialysis Patients with Diabetes,” on pages 856–866.