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Introduction: The Reverse Epidemiology Controversy

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The rising tide of chronic kidney disease (CKD) has resulted in an increasing number of patients starting dialysis, placing an ever greater burden not only on the nephrology community, but also on the whole society. Patients receiving maintenance dialysis have a mortality rate surpassing that of many cancers, with a large proportion of these deaths occurring from cardiovascular causes. Treating cardiovascular disease in dialysis patients has thus become the main focus for everyday nephrology practice. It took decades since the initial conception of the Framingham study to develop paradigms for treatment of cardiovascular disease in the general population. It may seem plausible to apply the same paradigms to patients with CKD, as long as there is reasonable proof to indicate that their response to such measures is similar to what we expect from other patients. Such proof would start by showing an association in observational studies between the risk factor(s) in question and an outcome, such as mortality, followed by clinical trials indicating improved outcomes following modifications of these risk factors.

The paucity of clinical trials in the field of nephrology has mostly left us with observational studies when trying to determine what our best clinical practices should be. It has been very confusing and frustrating to nephrologists that a significant body of observational research indicated an association between the “classical” cardiovascular risk factors (such as obesity, hypertension and high cholesterol) and mortality in dialysis patients that is opposite to what we see in the general population. This phenomenon, also called “reverse epidemiology” or “risk factor paradox,” resulted in an ongoing debate about the plausibility of the associations and the applicability of these findings in everyday practice.

This issue of *Seminars in Dialysis* provides in-depth review and debates of the questions surrounding the phenomenon of reverse epidemiology in CKD. The obesity paradox is debated by Schmidt and Salahudeen on the one hand and Kwan and Beddhu on the other,

with Abbott et al. discussing the role of obesity in patients on peritoneal dialysis. Baigent et al. and Wan et al. discuss their viewpoints on treating high cholesterol in dialysis, with Kronenberg et al. providing an interesting addition in their paper on the kinetics of atherogenic lipoproteins in hemodialysis patients and with Scholze and Tepel discussing the role of leptin in reverse epidemiology. Drs. Lacson and Lazarus give an assessment of the role of blood pressure in dialysis survival, with Foley and Agarwal providing the counter-argument. Opposing viewpoints regarding the importance of homocysteine lowering in dialysis are expressed by Suliman et al. and by Zoccali et al. The presence of reverse epidemiology in other patient groups is discussed by Horwich and Fonarow and by Kovesdy and Anderson. The reversal of reverse epidemiology is discussed in two papers: Pauly and Chan examine the effect of daily nocturnal hemodialysis, and Chavalitdhamrong et al. review the impact of kidney transplantation. Balakrishnan et al. overview issues related to the genetics of reverse epidemiology in chronic dialysis and Agodoa and Eggers examine survival paradoxes in the context of racial and ethnic disparities in end-stage kidney failure. To conclude the issue, Levine et al. and Kalantar-Zadeh debate the merits of reverse epidemiology. Finally, Kopple provides the epilogue by trying to reconcile traditional and altered risk factor patterns in dialysis patients.

The papers presented in this issue represent by far the most exhausting review of what has been called reverse epidemiology in CKD; we hope it will lead to a clearer understanding of what has become not only an emerging research front but also a source of frustration for the practicing nephrologist. There is broad agreement that clinical trials will prove who is right or wrong on these issues; we can only hope that the field of nephrology will ultimately develop the knowledge that will help us provide the right answers for our patients and improve their survival.