Editorial

Chronic Kidney Disease Prevalence and Treated End-Stage Renal Disease Incidence: A Complex Relationship

Bénédicte Stengel* and Cécile Couchoud†

*INSERM U780, Research Unit in Biostatistics and Epidemiology, IFR 69, University Paris XI, Villejuif, and †The French Rein Registry, National Coordinating Center, Biomedecine Agency, Saint-Denis, France

The marked disparities in the incidence of treated ESRD worldwide (1,2) are widely known. Among them, the persistent high gap between the United States and western Europe is particularly striking, with rates two to three times higher in the United States: 338 per million population (*versus* 90 [Finland] to 170 [Germany]) in 2003 (3,4). Whether these disparities reflect differences in risk factors and prevalence of chronic kidney disease (CKD) between the two continents rarely has been investigated. CKD prevalence in US adults is known from the National Health and Nutrition Examination Surveys (NHANES) (5), but such population-based studies are scarce in Europe (6,7).

In this issue of *JASN*, Hallan *et al.* (8) report on CKD prevalence in Norway, on the basis of data from the second Health Survey of Nord-Tronlag County (HUNT II), a large population-based, cross-sectional survey that includes 65,181 adults (20 yr and older). Surprising, although incidence of treated ESRD in Norway (9) is one third that of US white patients, CKD prevalence was very similar in both populations. More precise, after standardization of estimated GFR (eGFR) between studies (10) and age and gender standardization for the US population, the prevalence of overall CKD stages 1 through 4 (11) was 9.3% in Norwegian adults and 11.0% in US white adults. Dividing adult ESRD incidence rates from national renal registries (3,9) by estimated prevalence for CKD stages 3 to 4 (eGFR < 60 ml/min per 1.73 m^2) produced a risk for treated ESRD among those who had reached these stages of 0.24% in Norway and 0.61% in US white individuals; that is, a risk 2.5 times higher in the United States. On the basis of this ecologic comparison, the authors argue that the higher risk for treated incident ESRD in the United States is not due to markedly greater prevalence of CKD but to a higher rate of progression from CKD to treated ESRD, a perplexing but not isolated finding.

Hsu *et al.* (12) first used ecologic comparisons to analyze the black–white disparities in treated ESRD incidence in the United States. They found a slightly lower prevalence of CKD stages 3 to 4 in black than in white individuals and a risk for entering renal replacement therapy (RRT) programs five times higher,

concluding that "the key to understanding racial differences in treated ESRD incidence lies in understanding differences in the progression from CKD to ESRD." Applying this method to the study of the relative trends in treated ESRD incidence and CKD prevalence, however, led them to different conclusions about the much faster rise in incident ESRD than in kidney diseases. They suggested that "more liberal entry into RRT programs and improved survival from competing causes among persons with CKD are the dominant contributors to the ESRD epidemic in the US" (13).

The same methods, the same findings, different interpretations. How, then, should we interpret the other ecologic risk ratios that can be drawn from Hallan's Table 4 (8): The ESRD risk that is 3.5 times higher in those who are younger than 60 yr *versus* those who are older than 60 in the United States and 6.2 times higher in Norway, or the higher risks for men than women? We need to be cautious in making causal inferences, even though ecologic studies that are based on aggregate measures actually may reflect phenomena that are true at the individual level.

The originality of this study lies in the extensive information that the authors gathered about population health, pre-ESRD care, and timing of dialysis, which they use to investigate potential explanations of disparities. First, because cardiovascular mortality was similar in both countries and life expectancy was higher in Norway, they ruled out survival from competing risks as an important contributor. Moreover, because point prevalence of CKD stages is a function of incidence (number of new CKD cases) and duration in each stage, similar population estimates may mask different situations: High CKD incidence with fast progression rate (short duration in each stage) or low incidence with slow progression rate (long duration in each stage). Diabetes, a major risk factor for the development and progression of renal disease, is more prevalent in American white individuals and is associated with nearly three times more cases of ESRD stages 3 to 4 than among Norwegians. It is likely to explain a substantial part of the overall increased ESRD risk in the United States. As Table 5 points out (8), 57% of the gap in RRT incidence between the two populations is associated with diabetes-related ESRD. This finding is consistent with several studies showing that diabetic ESRD accounts for many of the geographic variations and trends in overall incident treated ESRD (1,2,14–16).

In contrast, hypertension is more prevalent and less controlled in Europe than in the United States (17), even though rate of hypertensive ESRD seems higher in the United States. However, Stewart et al. (18) recently showed that community hypertension levels were not correlated with incidence of so-called hypertensive ESRD. Beyond the unresolved issue of misclassification in the absence of renal biopsy, it has been hypothesized that obesity and insulin resistance may be more important than essential hypertension in hypertensive ESRD (19). Because obesity, particularly morbid obesity, was recognized recently as a risk factor for ESRD and is far more prevalent in the United States than in Norway, it may play a role in the increased risk among Americans (20–22).

In addition, Hallan et al. found that predialysis care is shorter in US white patients, who also enter RRT in poorer nutritional condition and with more anemia than Norwegians. This underlines the possible role of suboptimal care in American pre-ESRD patients in explaining their faster progression to ESRD. However, the authors lacked information about the use of renin-angiotensin system inhibitors, which is very important for renal protection. Their large-scale use may lead either to underestimating the prevalence of CKD stages 1 to 2, because of their antiproteinuric effect, or, conversely to overestimating the prevalence of stages 3 to 4, particularly in the elderly, because these drugs tend to induce an hemodynamic decrease in GFR levels. They also relied on identical mean ages and GFR levels at RRT initiation to rule out variations in RRT acceptance rates as an explanation for the higher ESRD incidence in the United States, but this conclusion may be a little hasty. Norwegian patients are fully reimbursed at any stage of the disease, but US patients are not: They are reimbursed only after acceptance into an RRT program. Having no or mediocre health insurance coverage may influence the timing of dialysis initiation and may affect treated ESRD incidence, although it is difficult to quantify (23). Finally, cultural differences also may play a significant role: American medicine is known for its aggressive approach toward, for example, BP control (24), favoring a "can-do" attitude over the supportive nondialytic therapies that are given greater attention in some European countries (25). In this context, it is worth noting that the disparity in US/Norway risk ratios varies according to age, as the authors point out: It is three times higher among those who are older than 60 yr but only 1.7 times higher in those who are ≤60 yr.

In conclusion, by exploring the ecologic association of treated ESRD with CKD and several risk factors for the development and progression of renal disease, Hallan et al. highlight the complex nature of this relationship. They point out the major role of diabetes and very likely also obesity in the higher ESRD risk in the United States. Because these two conditions are increasing in Europe, we can expect ESRD incidence to rise here as well. They also point out the potential role of suboptimal pre-ESRD care in the United States, although the association may be more ambivalent. Moreover, uncertainty about whether differences between countries are based on ESRD or treated ESRD rates suggests that our understanding of geographic variations and trends would be improved by considering all CKD stage 5 (GFR <15) patients, regardless of whether they are on dialysis in renal registries. Further population-based studies also are needed to evaluate the true burden, determinants, and outcome of CKD in various populations.

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