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# **The timing of dialysis initiation affects the incidence of renal replacement therapy**

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## **Abstract**

### **Background**

**Variations in the timing of dialysis initiation may explain some geographical variations in RRT incidence, but this effect has never been quantified.**

### **Methods**

**Using data from the French Rein registry, we quantified the association between RRT incidence in 2006–2007 and median eGFR values before starting dialysis at the administrative district level with geographically appropriate methods.**

### **Results**

**Crude RRT incidence varied from 80.4 pmi to 238.6 pmi between administrative districts, and median eGFR at dialysis initiation from 5.9 to 11.8 ml/min/1.73m<sup>2</sup>. Age and sex-adjusted RRT incidence associated with a 1.2 ml/min/1.73m<sup>2</sup> increase in median eGFR rose 8% (4%–13%) before and 9% (5%–13%) after controlling for the effect of 9 potential socioeconomic and medical risk factors.**

### **Conclusions**

**The impact of increased eGFR at initiation should be taken into account in guidelines recommending earlier dialysis start.**

**MESH Keywords** Adult ; Glomerular Filtration Rate ; Humans ; Incidence ; Middle Aged ; Renal Dialysis ; Renal Replacement Therapy ; statistics & numerical data ; Time Factors

**Author Keywords** Epidemiology ; ESRD ; glomerular filtration rate ; incidence ; spatial analysis

## **INTRODUCTION**

In the last decade, incidence rates for renal replacement therapy (RRT) for end-stage renal disease (ESRD) have increased worldwide. Simultaneously, dialysis has tended to start earlier, although the timing of initiation remains controversial (1 ,2 , 3 ,4 ,5 ,6 ,7 ,8 ,9 ,10 ). In the US the percentage of patients starting dialysis with an estimated glomerular filtration rate (eGFR) greater than 10 mL/min/1.73 m<sup>2</sup> more than doubled from 1996 through 2005, from 25 to 54%. Starting patients at a higher eGFR may increase RRT incidence because some of these might have died in the interval between when they started RRT and when they would have done so with a lower threshold eGFR level (11 ). But this effect has never been quantified.

Although incident rates vary widely between countries (12 ,13 ,14 ), international comparisons require careful consideration of medical and non-medical factors that may contribute to these variations. Access to treatment, health spending, and resources explain a large part of these disparities. Exploring geographical patterns of RRT incidence within one single country may partially avoid these difficulties and facilitate the study of other determinants, including clinical practices.

We therefore quantified the association between eGFR level at dialysis initiation and RRT incidence rate in 71 French administrative districts, adjusting for potential explanatory variables (15 ).

## **MATERIALS AND METHODS**

Information about patients with incident ESRD came from the French REIN registry, described in detail elsewhere (16 ). We extracted data for all patients with incident ESRD from January 1, 2006, to December 31, 2007, in 71 administrative districts (covering 76% of the French population). Information included the patient's age, sex, district of residence, mean travel time to dialysis center and glomerular filtration rate (eGFR) estimated with the simplified MDRD equation at RRT start. The median value of eGFR at dialysis initiation was calculated for each administrative district.

Administrative districts were characterized by 9 different indicators, all potential confounders (15 ): rurality (population density), precariousness (proportion of people aged 20–59 years receiving minimum guaranteed income allowances), morbidity-mortality (age-adjusted cardiovascular mortality rate, age-adjusted rate of premature mortality due to alcohol in men, age and sex-adjusted prevalence of treated diabetes), health-care resources and supply (number of specialists and of nephrologists per 100 000 inhabitants, proportion of patients whose mean travel time to a dialysis centre exceeds 45 minutes) and clinical practices (proportion of incident patients older than 85 years).

A hierarchical random-effects Poisson regression model with spatially structured residuals (17 ,18 ) was used to investigate the association of the indirect age-and-sex-standardized incidence ratios with median eGFR at initiation. A multilevel model was used to take regional and administrative district variability into account. Associations between RRT incidence and eGFR were examined before and after controlling for the effect of other significant characteristics in multivariable models and are expressed as rate ratios of incidence associated with an increase of 1 standard deviation and their 95% credibility intervals. Models were fitted with an iterative stochastic algorithm in WinBUGS V.1.4.3 (19 ,20 ). Philcarto 5.05 (<http://philgeo.free.fr>) and the open source vector graphics editor Inkscape, with Jenks discretisation, produced all maps.

## RESULTS

This analysis covers 12,865 patients who began dialysis between 2006 and 2007 in the 71 administrative districts, for a mean number of 181 new patients (range: 19–812). The crude district RRT incidence rate varied from 80.4 pmi to 238.6 pmi (Figure 1 ). Rates were highest in the northeast and south and lowest in the west and east. Three administrative districts (Haute-Marne, Loir-et-Cher and Ardèche) had unexpectedly high rates.

The median eGFR at dialysis initiation varied from 5.9 to 11.8 ml/min/1.73m<sup>2</sup> (mean 8.2, SD 1.2) across administrative districts ( Figure 2 ). Age- and sex-adjusted RRT incidence associated with a 1.2 ml/min/1.73m<sup>2</sup> increase in median eGFR rose by 8% (95% credibility interval: 4%–13%) before and 9% (95% CI: 5%–13%) after controlling for the effect of 9 potential socioeconomic and medical risk factors.

The spatial pattern of RRT incidence is nonetheless identical to that of eGFR because other factors, such as diabetes prevalence, also explain geographic variations of RRT incidence.

## DISCUSSION

This study shows significant geographical differences in RRT incidence in 71 French administrative districts and an ecological association between median eGFR at RRT start and RRT incidence. Some studies have investigated the possible determinants of these variations (21 ,22 ,23 ,24 ,25 ,26 ), but to our knowledge this is the first report to quantify with geographically appropriate methods the contribution of early dialysis initiation. Moreover, the 3 administrative districts with unexpectedly high incidence rates (over 210 pmi) all had higher median eGFR levels at RRT start (over 10 ml/min/1.73m<sup>2</sup>).

Lower RRT incidence associated with lower eGFR at initiation reflects mortality associated with decreasing eGFR. Whether all patients with ESRD (eGFR < 15 ml/min/1.73 m<sup>2</sup>) who die before starting RRT would benefit from dialysis, nevertheless, remains controversial. Earlier studies showed better outcome with early start (3 ,9 ), but more recent ones tended to observe the opposite (4 –8 ). Based on Rein registry data, we have recently shown that age and comorbidity strongly determined the level of kidney function at dialysis start and explained most of the association of poor survival with greater eGFR(2).

However, the trends towards older new patients with greater comorbidity and clinical conditions, such as uncontrolled heart failure, may encourage nephrologists to continue starting dialysis at higher eGFR levels. The impact of prevention programs that slow the progression of chronic renal disease may thus be counterbalanced by earlier initiation.

Earlier initiation may increase costs because more patients will be treated by dialysis. Inversely, timely initiation may attenuate the complications of chronic renal failure and consequently reduce total cost (3 ,10 ). An appropriate medico-economic study is warranted to answer this critical question and to quantify the implications of early start recommendations for healthcare funding.

## Conclusion

This study shows that increased eGFR at initiation may have a substantial impact on RRT incidence. This should be taken into account in guidelines recommending earlier dialysis start and considered for healthcare planning.

## Acknowledgements:

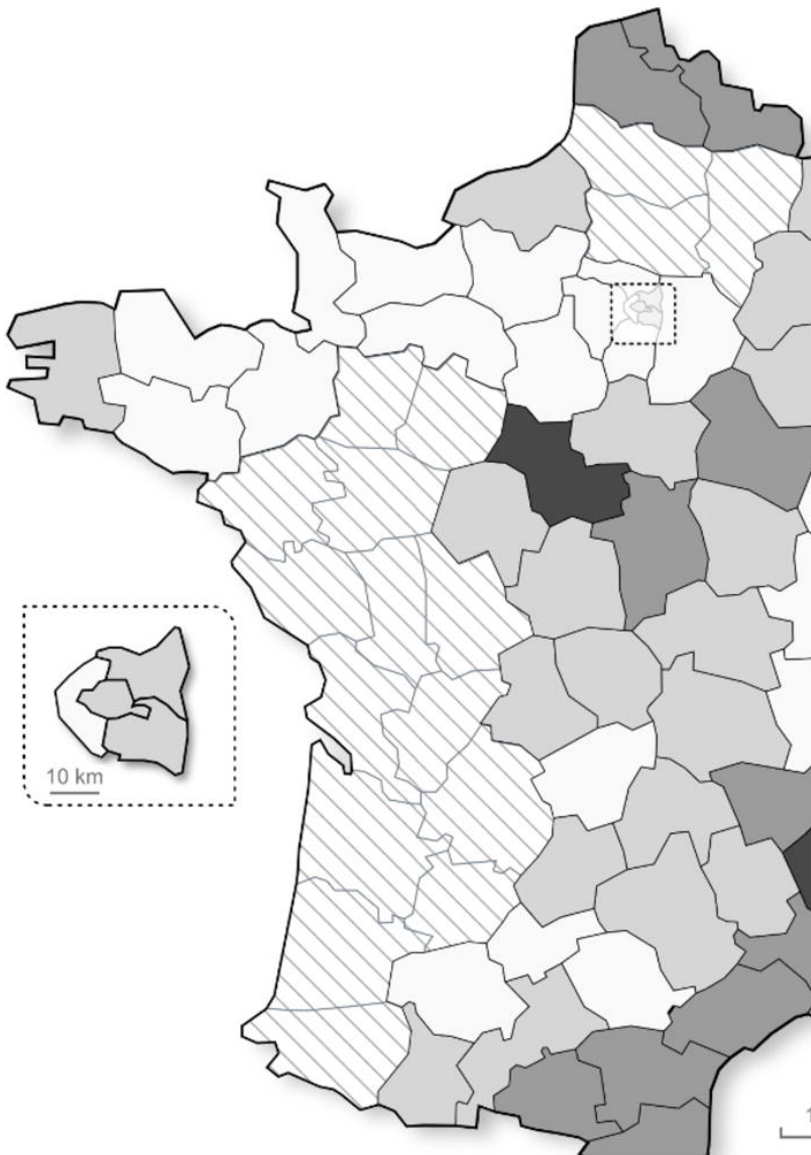
We acknowledge all registry participants, especially to the nephrologists and the professionals who collected the data and conducted the quality control. The dialysis center participating to the registry are listed in the annual report : <http://www.agence-biomedecine.fr/article/142>

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**Figure 1**

Geographical distribution of the crude RRT incidence by administrative districts



**Figure 2**

Geographical distribution of the median eGFR at dialysis initiation by administrative districts

