Author's response to reviews

Title: Impact of prior CKD management in a renal care network on early outcomes in incident dialysis patients: a prospective observational study

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Author’s response to reviews: see over
Responses to comments from Dr Levin

Comment 1:
We agree with Dr Levin’s remark on that point. Therefore, we added the following sentence in the patients and methods section (page 5): “There were standardized protocols for monitoring the patient’s clinical and biological status. The frequency of monitoring was based on the level of severity of CKD. To avoid losing sight of patients, they were contacted by telephone by members of the coordination of the network when they were not attended to a scheduled consultation. Educational sessions were proposed to the patients on a voluntary basis. The educational sessions and materials were built according to the French guidelines on patient’s education. Some cardiovascular risk factors, like Blood Pressure control and how to reach optimal blood level of cholesterol were specifically addressed during the educational sessions”.

Comment 2:
We chose the period around the start of dialysis for several reasons:
- It is a period where dialysis patients are the more prone to die, according to the report of French registry REIN: indeed the annual mortality rate in the whole population of French dialysis patients is close to 17%.
- In addition, suboptimal care during the period just preceding the enter in dialysis can have serious consequences for patients with CKD stage 4-5: delayed inscription on renal transplant waiting list, start the hemodialysis treatment with a catheter access whereas a AVF was feasible (which means an increased risk of infection), the risk of occurrence of an acute renal failure or of a severe electrolytic trouble, etc.
- Finally, according to the results of the REIN registry, it seems reasonable to assume that there is a potential for improving the management of patients during this period: indeed, 10% of patients started the dialysis treatment in the intensive care unit, approximately 40% of patients haven’t had a creation of AVF or had underdeveloped AVF and approximately 43% of patients had a haemoglobin below 10 g/dl.

Therefore, we added the following sentence in the Patients and Methods section (page 6):” We chose the period just around the start of dialysis because dialysis patients have the greatest mortality rate during the first year of dialysis treatment. Moreover, suboptimal care during the period just before the start of dialysis can have serious consequences for patients with stage 4-5 CKD and we assumed that there is a potential for improving the management of patients during this period. Finally only patients who actually started dialysis treatment were included ”

Comment 3:
In our study, the average GFR of patients at inclusion were similar in both groups. Because patients of the network group had slower progression, the higher average eGFR (calculated by using MDRD equation) in this patients group was expected. The question to know if that could have had an impact on the primary outcome is difficult to determine. However, the results of the IDEAL study suggest that the beginning of dialysis treatment at higher GFR (9 vs 7.2 ml/min per 1.73m2 using MDRD) has no impact on all-cause mortality during a median follow-up 3.6 years. Moreover, by looking at the survival curves of the IDEAL study, we can see that it seems quite unlikely that there was a difference on the 1-year survival. This suggests that the effect of the dialysis start at higher GFR on the primary outcome is probably negligible, even if we don't know the relationship between this parameter the occurrence of cardiovascular events in the first of dialysis.
Finally, the rate of patients starting hemodialysis treatment with effective AVF was the same in both groups (74% vs 81%; p=NS) as the rate of patients who started dialysis treatment in an unplanned way, which actually means because of an acute condition (25% vs 37%; p=NS as specified in the table 4).

We added the following sentence on this subject in the discussion section: "This difference in average eGFR at dialysis initiation has had probably no impact on the primary outcome and on the one-year mortality rate. Indeed, the IDEAL study showed that there were no difference in the one-year mortality rate between two randomized groups of patients who started dialysis respectively with 9 and 7.2 ml/min per 1.73m2 of average eGFR. Even if the impact of this difference is not known on the occurrence of cardiovascular events during, it seems unlikely that there could be an impact on the primary outcome of our study."

Comment 4:
We wrote in the page 12 of the manuscript that the care given to the patients of the control group were of high quality about the creation of a functional dialysis access. To avoid confusion for the readers on this point, we change the sentence as followed: "This occurred despite a higher proportion of patients with usable and sustainable access for first dialysis in the control group comparatively to the mean proportion in the REIN registry (69.2% vs 63%) [3], that suggests a high quality of care for the creation of dialysis access."

Comment 5:
We added the following sentence in the limitations section of the discussion (page 15): “Finally, one other limitation to mention is that our study was only interested by patients with stages 4-5 CKD. It can be speculated that the results could have been different with patients who wouldn’t have started dialysis (being treated only conservatively) or in patients with less severe CKD (i.e. stage 3 CKD)."

Comment 6:
We changed the conclusions as followed (pages 15-16): "In conclusion, our study shows that a dedicated renal cares network based on a distributed design is effective to decrease the rate of hospitalizations either in the year before and after dialysis initiation. Moreover, it could lower the slope of GFR decrease in patients with advanced CKD. Although no effects of the network were observed concerning the primary endpoint, this could result from a short follow-up period or being related to the CKD stages of the included patients. These results suggest that the management of patients with CKD in a renal care network could improve some of the patient’s outcomes but further studies are needed to confirm this positive effect."

Minor comment 1: the word “exposition” was changed to “exposure” (page 11)

Minor comment 2:
We added the following sentences in the discussion:
- Page 15, line 1: "French data network REIN showed that the risk of death is highest in the first year after the start of dialysis treatment (17% for the whole population), especially in older patients".
- Page 15, line 6: “Moreover, the French public health system, as in several countries, is actually subject to an economic pressure because the resources allocated tend to become limited and care cost is becoming more expensive (due to the aging of the population and to several others reasons like incoordination of some provided care). Therefore care network could also help to reduce the costs related to the management of ESRD, which is presently crucial because it is a costly disease.”
Responses to comments from Dr Fox:
Dr. Fox highlights the number of patients, which is claimed to be insufficient. Concerning the statistical power analysis, we endorse the remark that we have been optimistic about the 75% of decrease of the primary outcome in the network group. However, the calculation was done properly with the assumption of the 20% occurrence of primary outcome based on the data from the French REIN network of ESRD patients (incident and prevalent patients) for the one-year mortality and on the article by Foley and colleagues (J Am Soc Nephrol 1998) for the incidence of CV events. Therefore, the number of patients included fitted correctly the initial assumptions. Moreover, we think that the occurrence of the primary outcome was clearly higher in the study than expected because we probably underestimate the true incidence of CV events in our population. Indeed, we included in the primary outcome more different sort of CV events than in the article by Foley et al. consequently, we can deduce that the positive effect potentially afforded by the network was distinctly overestimate because more events should have made this effect easier to detect.

The second comment by Dr Fox is probably a misunderstanding. Indeed, the study is a cohort-matched study with the patients of the group who has been matched for age, sex and proportion of diabetic patients (as specified in page 6 of the revised manuscript). Therefore, the proportion of diabetic was 22.5% in each group (control and treatment) as showed in table 1. In this case, the comparison between the two groups is, in our opinion, relevant to test the effect of network on patient’s outcomes. What we highlighted, page 8 of the manuscript, is that there is less diabetic patients in the population of 160 patients included in the study, than in the whole population of patients included in the French REIN Registry of ESRD patients (33.8%).

Responses to comments from Dr Gilbertson:
We read the manuscript carefully in order to correct grammatical mistakes and improve the English editing. We also change the figure 3 and labelled properly the two lines. Finally, we agree with the comment about the assumption made about the network effect on primary outcomes, which was probably a bit too optimistic.